UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF RALPH ZIPPER, M.D., FACOG, FPMRS

I have been asked to provide expert opinions and testimony concerning the safety and efficacy of Ethicon's PROSIMA Anterior, Posterior and Combined Pelvic Floor Repair Systems and the PROLIFT Total, Anterior and Posterior Pelvic Floor Repair Systems. The opinions expressed herein are made to a reasonable degree of medical certainty or probability and are based on my knowledge, training and experience, and my independent investigation which included an in-depth and thorough review of peer-reviewed literature, Ethicon's internal documents and the depositions of Ethicon's current and former corporate employees.

MEDICAL TRAINING BACKGROUND AND QUALIFICATIONS

I am board certified in Female Pelvic Medicine and Reconstructive Surgery (FPMRS) and Obstetrics/Gynecology. I received my medical degree in 1992 from The Mount Sinai School of Medicine of the City University of New York. In 1996, I completed my fellowship in the field of Obstetrics/Gynecology at the John Hopkins Hospital, Department of Gynecology and Obstetrics, Baltimore, Maryland. My practice

of medicine has been dedicated to Urogynecology, FPMRS, for eighteen years. I am the president and director of Zipper Urogynecology Associates (ZUA), one of the busiest and most comprehensive private practice tertiary FPMRS referral centers in the U.S. Each year our team evaluates and treats over 2 thousand new patients. Over the last ten years I have trained over one thousand urologists and gynecologists in the techniques of prolapse and incontinence surgery.

Over the last 18 years I have performed over one thousand mesh and biologic tissue implantations pelvic organ prolapse procedures and a similar number of native tissue prolapse surgeries. . I have experience implanting most major mesh kits and as well as self tailored mesh and biologic grafts.

In addition to my role as a urogynecologist at ZUA, I am also currently serving as the President of Zipper Urogynecology Associates, the CEO of Uroshape, LLC (Develops laser technology for FPMRS), The CEO of an Radio Frequency Surgical device company, The President of Afterglow, LLC (Develops FMPRS technology for Sexual Dysfunction and Pelvic Pain), and the CEO of Zipper Brothers Films, LLC (Documentary Film Company and Academy Award Winner). I am also actively providing C-level consulting services to a publically traded monoclonal antibody Pharma company. I have authored fifteen relevant patent applications and have been issued multiple patents relevant to the field of pelvic reconstructive surgery which are published by the United States Patent and Trade Office.(table 1)

Relevant to this litigation, between the years of 1998 and 2008, I served as the Keynote Speaker on Pelvic Reconstruction Surgery at the annual National Sales Meeting for both C.R. Bard and American Medical Systems. I also was also hired to lecture

physicians at national meetings on prolapse and incontinence surgery by both C.R. Bard and Coloplast. Additionally, Coloplast commissioned me and Dr. Neeraj Kohli to write an abstract on the NovaSilk mesh product. This was presented at IGUA in or about 2008. Additionally, I served as a product development consultant to Boston Scientific. I met with Coloplast engineers and patent council to discuss my t of novel methods and devices for the treatment of stress urinary incontinence and pelvic organ prolapse. During this period of time Coloplast paid to hold me in a "no-shop" agreement. I served as a physician trainer for C.R. Bard for many years. During these years over three hundred physicians from across the United States were sent by C.R. to watch me use the C.R. Bard prolapse and incontinence products. During this time C.R. Bard also sought my opinion on product development including the licensing and or purchasing of mesh products from inventors and manufacturers.

As a private independent consultant, I have worked closely with engineers to develop devices including slings for the treatment of stress urinary incontinence, methods for the treatment of stress urinary incontinence, and mesh products and methods for the treatment of pelvic organ prolapse, many of which were subsequently deployed and sold by foreign and U.S. medical device companies. In this same role, I worked extensively to develop instructional materials and marketing materials for prolapse mesh and incontinence products. Over one thousand hours were spent in these endeavors that resulted in commercialization.

As the president and Chief Operating Officer of a Bipolar Radio Frequency medical device company with an existing market clearance, some of my responsibilities include supervision and vetting of ongoing regulatory initiatives, development and supervision of

ongoing labeling, supply chain, contract manufacturing, supervision of conformity attainment, supervision of all phases of R&D including engineering, bench and animal testing, and clinical trials, and KOL contracting. As President of Uroshape LLC, I have many similar responsibilities.

I am familiar with the type of information that should be communicated to surgeons so that surgeons can make reasonable informed choices when considering medical products. I have read and am familiar with the Instructions for Use ("IFU"), sales and marketing materials, and physician training materials, prepared by Ethicon for its pelvic floor and incontinence products. I have also reviewed the labeling for a multitude of pelvic floor products and incontinence products marketed by other companies including the labels of products I have and have not implanted in my practice of FPMRS.

A current copy of my Curriculum Vita is attached as Exhibit "A". A current copy of my Fee Schedule is attached as Exhibit "B". A list of my court testimony and depositions is attached as Exhibit "C" as well as my fee schedule. In addition to my medical training, background and experience, the documents and materials I relied upon for this report are contained in Exhibit "D". Additionally, I relied upon those materials cited in this report and cited herein.

THE IMPORTANCE OF NORMAL VAGINAL ANATOMY

There is perhaps no organ in the human body more important than the vagina. Obstetricians often jest that the heart's purpose is to pump blood to the vagina and the brain's purpose is to keep it safe. Human existence is predicated on propagation and the propagation of the human species is uniquely dependent on the female urogenital organ, the vagina. Yes it is true that other species propagate in a similar fashion to humans. Yet

human propagation is much more complex. The perpetuation of the human genome is in no small way predicated on the success of family unit. The human male-female bond created by the intimacy of sexual experience is part of the glue of marital relationships and long-term partnerships and satisfaction with sexual relationships has been shown to be significantly associated with better, more stable, happier marriages. The loss of this intimacy can undermine this relationship and disrupt the entire family unit.[1] Numerous researches have demonstrated the association between sexual dysfunction, marital problems and divorce.[2]

A normal vagina is not only vital to human relationships and the family unit; it is necessary to maintain normal bowel and bladder function. The connective tissues and muscles that support the vagina coincidentally support the bladder, rectum, and uterus. The bladder rests on the anterior wall of the vagina, the rectum rests on the posterior wall of the vagina and the uterus is supported at the top or apex of the vagina. Weakening of the supporting tissues of the vagina results in vaginal hernias that allow protrusion of the bladder, bowel, and uterus. These vaginal hernias are referred to as ***Pelvic Organ Prolapse***

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[1] *See* Atwood, J. D., & Dershowithz, S. (1992). Constructing a sex and marital therapy frame: Ways to help couples deconstruct sexual problems. Journal of Sex and Marital Therapy, 18, 196–219; Spence, S.H. (1997). Sex and relationships. In W. K. Halford & H. J. Markman (Eds.), Clinical handbook of marriage and couples interventions (pp. 73–105). New York: John Wiley.

[2] *See for example*, Bakhshayesh, A., &Mortazavi, M. (2009). Relationship Satisfaction, Sexual Health and Marital Satisfaction in Couples. Applied Psychology, 3: 4 (12): 85-73; Ali-akbari Dehkordi, M. (2010). Relation between Women's Sexual Function and Marital Adjustment. Journal of Behavioral Sciences , 4:13, 199-206; Lau, T.F. J., Yang, X., Wang, Q., Cheng, Y., Tsui, Yi. Hi., Mui, W.H. L., & Kim, H. J. (2006). Gender Power and Marital Relationship As Predictors of Sexual Dysfunction and Sexual Satisfaction among Young Married Couples in Rural China: A Population-Based Study, Urology, 67(3):579-585; Chen Yeh, H., Lorenz, O. F., Wickrama, K.A.S. Conger, D. R., & Elder Jr. H. G. (2006). Relationships among Sexual Satisfactin, Marital Quality, and Marital Instability at Midlife, Journal of Family Psychology , 20(2):339-343; Trudel, G., & Goldfarb, M. R. (2010). Marital and sexual functioning and Dysfunctioning, Depression and Anxiety, Sexologies, 19(3):137-142. *See also*, Ata Shakerian, Ali-Mohammad Nazari, Mohsen Masoomi (2014). Inspecting the Relationship between Sexual Satisfaction and Marital Problems of Divorce-asking Women in Sanandaj City Family Court. Procedia - Social and Behavioral Sciences 114 (2014) 327 - 333.

("POP") Vaginal childbirth is perhaps the greatest risk factor associated with the development of Pelvic Organ Prolapse. Hysterectomy and age are other common risk factors. The lifetime risk of POP may be as high as 30%.[3] Fortunately, the majority of women with POP will never become symptomatic.[4]

Symptoms of pelvic organ prolapse can include pressure, lower back discomfort, difficulty with urination, difficulty with defecation, irritation, or bleeding. When pelvic organ prolapse becomes symptomatic, many women will opt for surgical intervention.

A. Pelvic Organ Prolapse Nomenclature:

To understand discussions on Pelvic Organ Prolapse one should be familiar with the nomenclature. Different types of POP commonly occur together, the nomenclature follows:

Cystocele: A hernia of the anterior wall of the vagina resulting in prolapse of the bladder into the vagina.

Rectocele: A hernia of the posterior wall of the vagina allowing the rectum to bulge into the vagina.

Enterocele: A hernia at the top or apex of the vagina allowing the small intestines to bulge into the vagina.

Uterine Prolapse or Procedentia: A hernia at the top or apex of the vagina allowing the uterus to prolapse into the vagina.

Vaginal Vault Prolapse: A hernia of the apex of the vagina in women whom have had a hysterectomy.

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[3] Milsom, I., D. Altman, M.C. Lapitan, R. Nelson, U. Sillen, D. Thom. ICS Committee 1. Epidemiology of Urinary (UI) and Faecal (FI) Incontinence and Pelvic Organ Prolapse. 2013.

[4] Svihra J, Svihrova V, Digesu A, Hudeckova H, Kliment J, Swift S, Khullar V., Dept. of Urology, Jessenius School of Medicine,. Dept. of Public Health, Jessenius School of Medicine, Dept. of Urogynecology, St. Mary´s Hospital, Dept. of Obstetrics and Gynecology, Medical University of South Carolina. "Prevalence and severity of pelvic organ prolapse in symptomatic and asymptomatic women in relation to age." ICS ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 85: Pelvic organ prolapse. Obstet Gynecol. 2007; 110(3):717–729.

Stages of POP (a simplified narrative of the standardized Pelvic Organ Prolapse Quantification, POPQ):

- **Stage One**: Prolapse remains greater than 1 cm above the vaginal opening.
- **Stage Two**: Prolapse that is within an area defined as 1 cm above the vaginal opening to 1 cm beyond (exterior) to the vaginal opening.
- **Stage Three**: Prolapse that is greater than 1 cm beyond the opening of the vagina but is less than 2 cm from compete vaginal eversion.
- **Stage Four**: Complete eversion of the vagina.

IV. THE TREAMENT OF PELVIC ORGAN PROLAPSE VERSUS THE TREATMENT OF PELVIC ORGAN PROPLASE SYMPTOMS

A. Native Tissue Surgeries

These surgeries, which use suture material to pull together the patients stretched and weakened tissues, have been utilized for hundreds of years with great success and limited complications. Examples of native tissue repairs include anterior colporrhapy (repair of a cystocele), posterior colporrhaphy (repair of a rectocele), and sacrospinous colpopexy (repair of vaginal vault prolapse). The majority of studies evaluating the efficacy of native tissue repairs have focused on partial anatomic recurrences rather than a recurrence of symptoms. One such RCT reported that only 30% of women undergoing anterior colporrhaphy remained with satisfactory anatomic results at 23 months. However, when this same study was reanalyzed for subjective success (improvement in symptoms), the data demonstrated that 95% of patients were no longer symptomatic.[5] Systematic reviews of the literature have confirmed that native tissue repairs are quite effective, as effective as

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[5] Weber AM, Walters MD, Piedmonte MR, Ballard LA. "Anterior colporrhaphy: a randomized trial of three surgical techniques." Am J Obstet Gynecol 2001; 185:1299–304; discussion 1304–6; see also, Chmielewski L, Walters MD, Weber AM, Barber MD. "Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success." Am J Obstet Gynecol 2011; 205:69.e1–69.e8.

mesh and other graft surgeries, and are associated with less bleeding, shorter operative times, and a lower incidence of post-surgical development of stress urinary incontinence and prolapse in other areas.[6]

B. Graft Augmentation Surgeries

C. HISTORY OF SURGICAL MESH

Synthetic polypropylene materials have been used since the 1950s to treat hernias within the abdominal region. However, as the use of synthetic mesh to treat hernias increased, so did reports of severe mesh-related complications. By the mid-1990s, researchers determined that the material used, pore size and elasticity were all critical characteristics that influenced the manner and extent in which the synthetic graft material would respond within a patient's body.[7]

Researchers – some of whom were working as paid consultants for Ethicon and Johnson & Johnson – determined that pores falling below 1000 microns (or 1mm) in all directions after implantation in the body (known as effective porosity) elicit a greater foreign body response and inflammatory reaction than mesh with pores greater than 1000 microns (or 1mm). It was determined that small pore meshes (meshes with pores less than 1000 microns after implantation) cause bridging fibrosis where the pores become filled with scar tissue, rather than healthy tissue. This results in all or nearly all of the mesh becoming encapsulated in a rigid scar plate. This excessive foreign body reaction (FBR)

[6]Christopher Maher, Benjamin Feiner, Kaven Baessler, CorinaSchmid. (2013). "Surgical management of pelvic organ prolapse in women." The Cochrane Library.

[7] See e.g., P.K. Amid, Classification of biomaterials and their related complications in abdominal wall hernia surgery, Hernia (1997) 1:15-21; Klinge et al., Shrinking of polypropylene mesh in vivo: an experimental study in dogs. European Journal of Surgery Vol. 164, Issue 12, pp 965-969 (Dec. 1998); Klinge et al., Foreign body reaction to meshes used for the repair of abdominal wall hernias, Eur J Surg. 165(7):pp 665-73 (July 1999); Klosterhalfen et al., Functional and morphological evaluations of different polypropylene-mesh modifications for abdominal wall repair, Biomaterial, 19(24), pp 2235-46 (Dec. 1998).

with associated inflammation causes extensive scaring in small pore meshes which leads to an unacceptably high rate of mesh-related complications including, but not limited to, infections, shrinkage, erosions, chronic dyspareunia and chronic pain.[8]

The innate immune system recognizes and attacks foreign material. This is known as the foreign body reaction (FBR). Different materials are associated with different degrees of FBR. In the best-case scenario, the material is associated with only a minimal FBR and a mild, short-lived FBR occurs. In the worst-case scenario, a chronic FBR occurs. We are all familiar with the signs of a FBR, redness, warmth, swelling, pain and loss of function. Indeed, medical students are given these words to memorize in Latin: rubor, calor, tumor, dolor, functio laesa.

As Dr. Cobb and his co-authors reported "[t]he long-term consequences of implantable polypropylene prosthetics are not without concern. The body generates an intense inflammatory response to the prosthetic that results in scar plate formation, increased stiffness of the abdominal wall, and shrinkage of the biomaterial."[9] Multiple investigators have demonstrated the dramatic difference between a repair performed with native tissue and suture compared to one performed with polypropylene mesh. The authors demonstrated that, unlike the native tissue repair, the ppm repair did not heal and continues

[8] Klinge et al., Shrinkage of Polypropylene Mesh in vivo: An Experimental Study in Dogs, Eur J. Sur 164 (1998); Klinge et al., Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model, Journal of Surgical Research 103, 208-214 (2002); Klosterhalfen et al., The Lightweight and large porous mesh concept for hernia repair (2005); Cobb et al. The Argument for Lightweight Polypropylene Mesh in Hernia Repair, Surgical Innovation, Vol. 12, No 1, (March) 2005: pp 63-69; Klinge et al. Demands and properties of alloplastic implants for the treatment of stress urinary incontinence, Expert Rev. Med. Devices 4(3), (2007); Muehl et al., New Objective Measurement to Characterize the Porosity of Textile Implants, Wiley Interscience (2007); Otto et al, Elongation of textile pelvic floor implants under load is related to complete loss of effective porosity, thereby favoring incorporation in scar plates, Society for Biomaterials (2013); Klinge et al, High Structural Stability of Textile Implants Prevents Pore Collapse and Preserves Effective Porosity at Strain, Biomed Research International, Vol 2015; Barone et al., The Impact of boundary conditions on surface curvature of polypropylene mesh in response to uniaxial loading, Journal of Biomechanics (2015).

[9] Cobb, et al., The Argument for Lightweight Polypropylene Mesh in Hernia Repair, Surgical Innovation, Vol. 12, No. 1(March), 2005: pp 63-69.

to behave like both an acute and chronic wound in perpetuity.[10] Although decreasing the inoculum (the amount of polypropylene) may decrease the severity of the FBR, the problem of the chronic FBR with ongoing acute and chronic inflammation persists and may even worsen.[11] Acute and chronic inflammation are associated with both pain and loss of function.[12] Indeed the most common complication reported in the FDA's systematic review of transvaginal mesh are those associated with inflammation: extrusion and pain.

Polypropylene implantation creates a strong FBR. As part of the FBR the body's white blood cells release powerful oxidizing agents including ionized oxygen, hydrogen peroxide and hypochlorite. These powerful oxidizing agents change the chemical composition and physical properties of the polypropylene mesh fibers. The oxidation of polypropylene mesh implants is many times greater than would be expected when exposed to room air.[13] This results in mesh degradation, worsening inflammation, loss of elasticity and contraction.[14] This contraction may be as great as 85% and continue for at least 9 years.[15] Even those studies frequently cited by purveyors of ppm have shown contraction in the range of 15 to 35% as well severe loss of elasticity.[16]

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[10] Id.

[11] Arnaud Clavé & Hannah Yahi & Jean-Claude Hammou & Suzelei Montanari & Pierre Gounon & Henri Clavé. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261–270.

[12] Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591.

[13] Timothy C. Liebert, Richard P. Chartoff, et al. Subcutaneous Implants of Polypropylene Filaments. J. BIOMED. MATER. RES. VOL. 10, PP. 939-951 (1976).

[14] C. R. Costello, S. L. Bachman, B. J. Ramshaw,2 S. A. Grant. Materials Characterization of Explanted Polypropylene Hernia Meshes. Journal of Biomedical Materials Research Part B: Applied Biomaterials. Published online 6 February 2007 in Wiley InterScience (www.interscience.wiley.com).

[15] Letouzey V, Deffieux X, Levailolant J, et al. Overview of transvaginal placement of reconstructive materials (surgical mesh or biografts) for treatment of pelvic organ prolapse or stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:S205.

[16] KamilSvabikeAloisMartaneJaromir lasata Rachid El-Haddad -Petr Hubka eM arketa Pavlikova.

SURGICAL MESH FOR THE TREATMENT OF PELVIC ORGAN PROLAPSE

Erroneously acquitting partial anatomic recurrences with subjective failures (believing that a small amount of recurrent POP, even though asymptomatic, was a problem), many thought leaders have endeavored to invent methods to augment the weakened native tissue. Although it is unclear when this endeavor began, the 1990s saw a small but growing number of expert urogynecologists and urologists performing transvaginal graft implantation. Some of these specialists utilized cadaveric tissue: allografts. Others experts utilized animal tissue: xenografts. A smaller number of specialists began using synthetic meshes.

The problems of inflammation, mesh contraction, abdominal wall rigidity, and mesh related pain that were well documented in the abdominal hernia literature should have raised substantial concern[17] to companies like Ethicon and Johnson and Johnson who were

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Ultrasoundappearancesaftermeshimplantation evidence of mesh contraction or folding? Int Urogynecol J (2011) 22:529-533. Dietz HP, Erdnaann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol. 2011;204:173.el-4.

[17] See Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan; 2(1):103-17; Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan; 2(1):103-17; Agresta F, Baldazzi G, Ciardo et al: Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone 25) for TAPP inguinal hernia repair. Surg Laparosc Endosc Percutan tech 2007, 17; 91- 94; Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia (1997)1:15-21; Bellon J, Honduvilla N, Jurado F et al: In vitro interaction of bacteria with polypropylene/ePTFE prostheses. Biomaterials, 2001 Jul; 22(14):2021-4; Bouikerrou M, Boulanger L, Rubod C et al: Study of the biomechanical properties of synthetic implanted in vivo. European. J. Obstet & Gynecol and Repro Bio 134: (2007)262-267; Klinge U, Klosterhalfen M, Muller A et al: Shrinking of polypropylene mesh in vivo: an experiment study in dogs, European Journal of Surgery Volume 164, Issue 12, pages 965–969, December 1998; Klinge U, Klosterhalfen B, Muller M et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg. 1999 Jul; 165(7):665-73; Klinge U, Klosterhalfen B, Birkenhauer V: Impact of polymer pore size on the interface scar formation in a rat model. J. Surgical Research 103, 208-214 (2002); Klosterhalfen B, Klinge W, Schumpelick V: Functional and morphological evaluation of different polypropylene- mesh modifications for abdominal wall repair. Biomaterials. 1998 Dec; 19(24):2235-46. Krause H, Galloway S, Khoo S et al: Biocompatible properties of surgical mesh using an animal model. Aust N Z J Obstet Gynaecol. 2006 Feb; 46(1):42-5; Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan; 22(1):47-52; Garcia M, Ruiz V, Godoy A, et al: Differences in polypropylene shrinkage depending on mesh position in an experimental study. American Journal of Surgery Vol 193, Issue 4, April 2007, p538-542; Cappelletti M, Attolini G, Cangioni G, et al. The use of mesh in abdominal wall defects. Minerva Chir. 1997 Oct; 52(10):1169-76; Klosterhalfen B, Klinge W,

considering using synthetic mesh devices in the vagina especially since those same problems in the vagina would have much graver consequences. Studies had demonstrated that the contraction of hernia mesh resulted in loss of abdominal compliance and pain.[18] Contraction and loss of vaginal stretch could create significant problems with sexual function. Additionally, the pelvis has a complex anatomy, an anatomy filled with nerves responsible for bowel function, bladder function, and sexual stimulation. Inflammation and contraction of pelvic tissues creates unique and debilitating problems never experienced with abdominal hernia repairs. Furthermore, abdominal hernia surgeries involve the placement of synthetic mesh through a clean incision with limited risk for bacterial contamination and infection. A vaginal incision is not considered clean, it is considered clean/contaminated, an incision with substantial risk of bacterial contamination.[19]

The goal of pelvic organ prolapse surgery is to resolve symptoms. Although commonsense would suggest that this would require a complete restoration of youthful anatomy, such is neither possible nor necessary. A modest reduction of POP typically results in high patient satisfaction. This is evidenced by the numerous randomized

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Hermanns B et al: Pathology of traditional surgical nets for hernia repair after long- term implantation in humans. [ABSTRACT] Chirugr 2000; 71:43-51; Seker D, Kulacoglu H. Long-term complications of mesh repairs for abdominal wall hernias. J Long Term Eff Med Implants. 2011; 21(3):205-18; Cobb W, Burns J, Peindl R et al: Textile analysis of heavy weight, mid-weight, and light weight polypropylene mesh in a porcine ventral hernia model. J Surgical Research 136, 1-7 (2006); Pandit A, Henry J. Design of surgical meshes - an engineering perspective. Technol Health Care. 2004; 12(1):51- 65; Pierce L, Grunlan M, Hou Y et al: Biomechanical properties of synthetic and biologic graft materials following long-term implantation in the rabbit abdomen and vagina. Am J Obstet Gynecol. 2009 May; 200(5):549.e1-8; Costello C, Bachman M, Grand, S, et al. Characterization of heavyweight and lightweight polypropylene prosthetic mesh explants from a single patient. Surg Innov. 2007Sep; 14(3):168-76.

[18] Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia (1997) 1:15-21.

[19] Astrid Vollebregt & Annet Troelstra & C. Huub van der Vaart. (2009). Bacterial colonisation of collagen-coated polypropylene vaginal mesh: are additional intraoperative sterility procedures useful, Int Urogynecol J (2009) 20:1345–1351.

controlled trials (RCTs) that have evaluated different POP surgeries for anatomic and symptomatic outcomes. These RCTs have failed to demonstrate higher patient satisfaction or improved quality of life following surgeries with greater degrees of POP reduction.[20]

C. Native Tissue Repairs versus Polypropylene Mesh Repairs of POP

The highest levels of scientific evidence are found in Randomized Controlled Trial ("RCT"). The most valued and reliable data comes from systematic reviews of a multiple RCT. Although clinical studies were not performed prior to the mass commercialization of transvaginal mesh kits, a number of RCTs and systematic reviews are now available. In 2011, the American Board of Obstetricians and Gynecologists (AGOG) published their Committee Opinion on the Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse.[21] The committee opinion was based on a review of the both the published systematic reviews of RCTs and observational studies as well as individual RCTs. They were unable to find data to demonstrate any superiority of PPM surgery compared to native tissue repairs of the posterior vagina and apex (rectoceles and apical prolapse). They were able to identify a single RCT that showed a small superiority with regard to anterior support following mesh surgery. However, there was no data to show a symptomatic advantage. The committee concluded:

> [T]here are insufficient data on the use of mesh for the posterior or apical compartments. The risk/benefit ratio for mesh-augmented vaginal repairs must balance improved anatomic support of the anterior vaginal wall against the cost of the devices and increased complications such as mesh erosion, exposure, or extrusion; pelvic pain; groin pain; and dyspareunia.[22]

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[20] Christopher Maher, Benjamin Feiner, Kaven Baessler, CorinaSchmid. (2013).Surgical management of pelvic organ prolapse in women. The Cochrane Library.

[21] Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse. (2011). COMMITTEE OPINION, Number 513 • December 2011, Committee on Gynecologic Practice. The American College of Obstetricians and Gynecologists.

[22] Id. at fn. 10.

Based on its review, ACOG recommended that "Pelvic organ prolapse vaginal mesh repair should be reserved for high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior compartment) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures." [23]

The Cochrane Collaboration is a not-for-profit international network of health practitioners and researches that promote evidence based medicine by performing high quality systematic reviews of predominantly randomized controlled trials. The Cochrane reviews are internationally recognized as the highest standard of evidence-based health care. In April of 2013 the Cochrane Collaboration published its systematic review of 56 randomized controlled trials of surgical operations for pelvic organ prolapse. Similar to the findings of ACOG, The Cochrane group found there to be no significant benefit of transvaginal PPM surgery for posterior and apical pelvic organ prolapse. Likewise, PPM was not associated with any superiority compared to native tissue surgery when surgery was performed for more than one compartment (e.g. combined rectoceles and cystocele surgery). PPM surgery resulted in an 11 percent reoperation rate whereas native tissue surgery had on a 3% reoperation rate. The risk of mesh erosion was as high as 18%. Although transvaginal PPM surgery of the anterior compartment (cystocele surgery) was associated with a lower incidence of patient awareness of recurrent POP, no superiority was noted with regard to quality of life (QOL). Blood loss, operative time, de novo (new onset) stress urinary incontinence, and new POP at the apex and posterior compartment

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[23] Id.

were all lower with native tissue surgery. Anterior compartment mesh surgery was associated with an 11% mesh erosion rate and 6.8% reoperation rate for such erosions.

In 2013, the American Urogynecologic Society published its position statement on the Restriction of Surgical Options for Pelvic Floor Disorders. They stated with regard to transvaginal mesh surgery that "it is our strong opinion that there is a subset of women with prolapse in whom the benefits outweigh the risk". There are no clear guidelines for identifying whom is such a candidate. All medical societies, manufacturers, and the FDA agree that transvaginal mesh is not superior to native tissue repairs in reducing symptoms of POP and is associated with inflammation and contraction that can lead to severe complications including chronic pelvic pain. It is also agreed that such complications can create the need for complete removal of the implant. I have personally trained over 1000 surgeons and am not aware of one that can successfully remove a contracted and inflamed transvaginal mesh.

THE HISTORY OF PROSIMA

On November 15, 2002, Dr. Carey filed his provisional patent for the procedure and device which was eventually purchased and commercialized by Ethicon and Johnson & Johnson as the PROSIMA.[24] Dr. Carey's patent was published on July 3, 2004.[25] In his published patent, Dr. Carey explained that a new device was needed because "the synthetic meshes currently in use [were] far from ideal as they ha[d] been designed principally for the treatment of anterior abdominal wall hernias."[26] Importantly, Ethicon's PROLIFT devices – manufactured using the same Gynmesh PS polypropylene material – was one of

[24] PCT/AU2003/001494,
[25] **WO2004045457 A1**
[26] *Id.* at ___

the devices on the market when Dr. Carey published this statement. To address the problems associated with the synthetic meshes on the market at that time, Dr. Carey's patent called for a two-armed, lightweight, flexible, nonwoven mesh material with pores measuring 3mm x 3mm (3000 microns x 3000 microns) in the central body and 1 mm x 3 mm) (1000 microns x 3000 microns) in the arms without any open interstices at the junctions between the respective strands to prevent mesh related infections.[27]

The only clinical data available prior to Ethicon placing the PROSIMA on the market was conducted by the inventor, Dr. Carey. Dr. Carey reported that no women in his study developed symptomatic or objective evidence of grade 2 (Balden-Walker classification) or more pelvic organ prolapse.[28] However, the study had significant limitations and only involved 49 women with a very short-term follow-up of only four weeks.

Dr. Carey's application eventually resulted in both a method and device patent.[29] On September 30, 2004, Dr. Marcus Carey sold his patent (the method and device that would be commercialized as PROSIMA) to Ethicon for a one million dollars ($1,000,000.00) and a royalty on worldwide sales caused by the commercialization of his method.[30] One half of the million dollars would be held until certain benchmarks were achieved. One hundred thousand dollars would be held back until Dr. Carey published a clinical study on the patented method in an internationally recognized peer reviewed

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[27] *Id.* at ____
[28] CITE THE STUDY OR BATES NUMBER OF THE STUDY HERE
[29] CITE
[30] ETH.MESH .09746846

journal. Four hundred thousand dollars would be held back until Ethicon made available for sale product covered by at least one claim of the patent in the U.S. or Europe. Ethicon estimated a market size for MINT (PROSIMA), based on $600 per kit, to be 270,600,000.[31] Based on this number, Dr. Carey's 2.5% annual royalty could be as high as 6.7 million dollars per year. In addition to said monies, Dr Carey would be 2,500 per day for consulting services including investigation and commercialization of products based on his invention. The consulting portion of this agreement appears to have continued for many years.

According to an internal document dated April 25, 2005, the goal of the PROSIMA/MINT project was to "[d]evelop a robust procedural kit for the general gynecologic surgeon entailing a less technically challenging, standardized technique to address pelvic floor repairs which will improve functional outcomes over traditional suture based repairs (colporrhaphy)."[32] The proposal stated that the new kit would be supported by clinical outcomes that demonstrate reduced recurrence and low complications and would target "non-specialized GYN surgeons" and patients with "stage 2 or greater anterior or posterior prolapse or those that are stage 1 symptomatic."[33]

On September 6, 2005, Kim Hunsicker, Ethicon's Director of Clinical Programs, sent an email to Ethicon colleagues confirming that Ethicon will be targeting non-specialists. She stated "discussed (PROSIMA) with the inventors and marketing and the main targets will be those doing non-mesh anterior and posterior repairs."[34] In the same month, internal Ethicon emails demonstrate that some of Ethicon's employees were

[31] ETH.MESH.07902335
[32] ETH.MESH.07902335
[33] CITE
[34] ETH.MESH.03048784

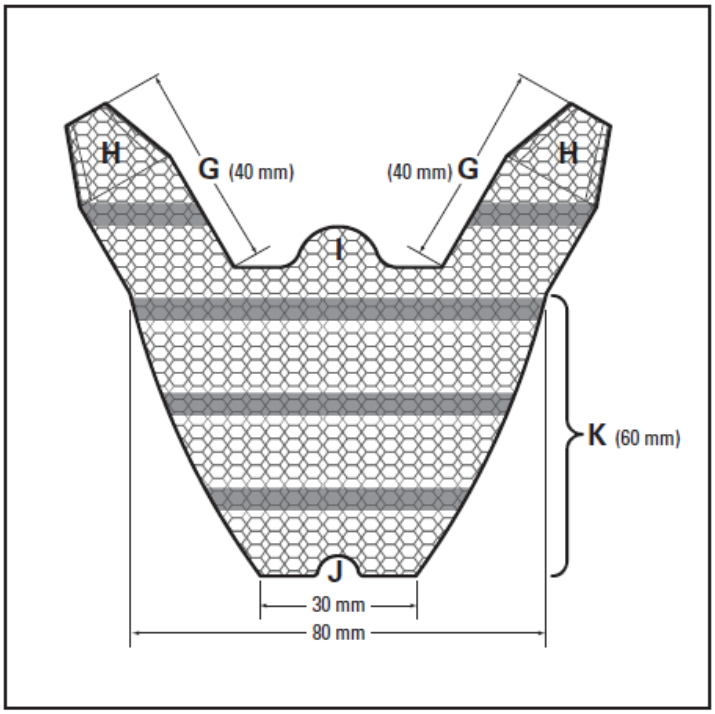
concerned that PROSIMA may not bring any benefit to the market place. In an email from Ethicon Medical Affairs Director, Martin Weisberg, Dr. Weisberg raised concerns that the inventor's study only showed non-inferiority to native tissue repairs and asked "[w]hy would we want to introduce a synthetic graft that does no better than native tissue?"[35] Several days later, Ethicon's World Wide Marketing Director, Allison London Brown wrote, "We need to show that we are providing some type of benefit on the new products we launch, otherwise what is the value to the customer."[36]

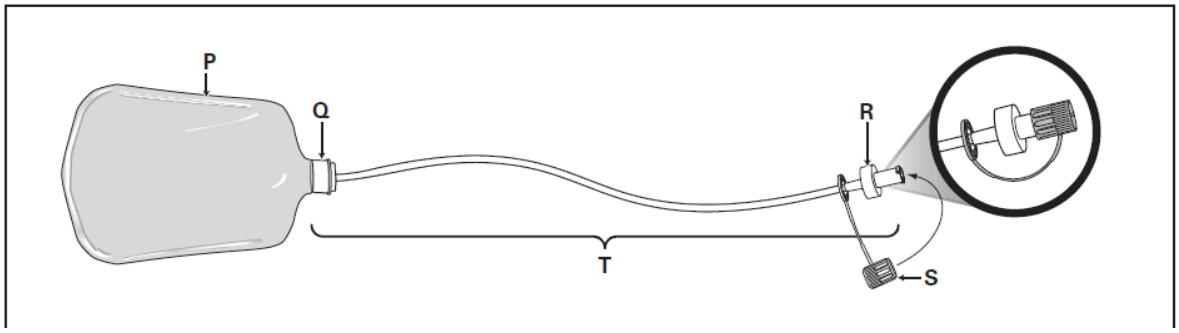
Despite the lack of adequate clinical data demonstrating that PROSIMA would be superior to and safer than alternative methods, a November 2005 PowerPoint presentation claimed that PROSIMA "w[ould] improve functional outcomes over traditional native and current flat mesh repairs. For patients it provides support and stabilization of vagina in the critical post-operative period of wound healing, improves wound healing, strength and reduces recurrence rate." [37]

On November 27, 2006, Ethicon filed its 510(k) application with the FDA claiming as its predicate devices the Gynemesh PS and the Silimed Vaginal Stent. On February 26, 2007, Ethicon received FDA clearance to market the PROSIMA device. [38] The PROSIMA Anterior, Posterior and Combined Pelvic Floor Repair Systems are manufactured out of Ethicon's Gynmesh PS polypropylene material.[39] While the PROSIMA device is manufactured by Ethicon using the same Gynemesh PS material used in Ethicon's PROLIFT device, the PROSIMA is different in that it has two arms instead of four, is used

[35] ETH.MESH.03048785
[36] ETH.MESH.03048783
[37] 112240.ppt
[38] FDA K063562
[39] PROSIMA IFU (NEED BATES NUMBER)

with an inflatable balloon intended to prevent post-operative bleeding, and the method of placement is different.[40]





Before even receiving FDA clearance to market PROSIMA, concerns were raised regarding the high failure rate observed in Dr. Carey's 12-month clinical study – a concern shared by Ethicon's Key Opinion leaders (KOLs) who felt that PROSIMA would not

[40] Images obtained from the PROSIMA IFU (CITE BATES NUMBER)

provide adequate apical, anterior or posterior support.[41,42,43,44] Ethicon grew concerned over the disappointing results of Dr. Carey's 12-month clinical results which demonstrated an unacceptably high failure rate.[45] This same internal document demonstrates that Ethicon was aware that lightweight and larger pore meshes were needed to reduce mesh shrinkage and the high rate of complications associated with devices like the PROLIFT and PROSIMA and that Ethicon had already developed a lightweight, large pore mesh using ULTRAPRO which had encouraging preclinical results "particularly for shrinkage reduction."[46]

On January 24, 2007, Allison London Brown informed her colleagues working on the PROSIMA product that the launch of the PROSIMA would be delayed because – according to her – "while we determined that the study was a strong proof of concept, it did not meet the full requirements for our launch needs, especially considering the substantial differences between the original study's product/procedure and the final commercial PROSIMA producdt. Ms. Brown indicated that Ethicon would conduct its own clinical study during the second quarter of 2007 and that Ethicon would wait for the 6 month clinical review before launching PROSIMA.[47]

On February 5, 2007, David Robinson emailed several of his colleagues concerning "good news" he received from Dr. Carey regarding his submission of his 12-month study manuscript that Dr. Carey submitted to BJOB . David Robinson acknowledged that he and

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[41] ETH.MESH.03049713
[42] ETH.MESH.03049945
[43] ETH.MESH.03912703
[44] ETH.MESH.00455676
[45] *Id.*
[46] *Id.*
[47] ETH.MESH.00455676

his colleagues were concerned with Dr. Carey because he had submitted the manuscripts to BJOG without allowing Ethicon to review it first and because of Ethicon's concerns related to the large number of patients who were lost to follow-up. Dr. Robinson reported that while BJOG responded that they wanted to publish Dr. Carey's article, it needed "a major re-write." According to Dr. Robinson "This seems to be the best of both worlds: we get the chance to revise the data...and we have the agreement from the journal that they will publish once they are happy with the manuscript."[48]

Ethicon's internal documents demonstrate that PROSIMA is not effective and is associated with an unreasonably high risk of complications.[49,50,51,52,53,54,55,56,57,58] For example, in an email dated April 12, 2008, Dr. Carey discusses a plan to confront concerns about the high rate of failure and complications associated with PROSIMA. Dr. Carey wrote that he was having a "sense of de javue. I recall when the MINT data first appeared there was initially a lot of concern about 85% success rate and a few cases of vaginal stenosis among other things." Dr. Carey discusses a plan to confront PROSIMA's problems which included, among other things, meeting to better "frame" the clinical data. As discussed elsewhere in my report, Dr. Carey was the inventor and had a substantial financial interest in the success of PROSIMA.

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[48] ETH.MESH.06148459
[49] ETH.MESH.04098598
[50] ETH.MESH.03162936
[51] ETH.MESH.05009194
[52] ETH.MESH.04569706
[53] ETH.MESH.10376374
[54] ETH.MESH.10416655
[55] ETH.MESH.08961175
[56] ETH.MESH.03466382
[57] ETH.MESH.05592152
[58] ETH.MESH.03721558

Judith Gauld writes to David Robinson and Johnathan Meek concerned that the clinical data had already demonstrated that PROSIMA failed and that Dr. Carey's suggestions would be interpreted as financially biased spin:

> We did state in the protocol that the study would be considered a failure if the failure rate had an upper 95% CI of less than 20% at 12 months. We have already failed that. I am concerned here that this look like **good bit of spin going on, and due to his commercial interest, this is not going to come over as objective as perhaps it should.**[59]

Despite this understanding, Ethicon continued to market PROLIFT and began selling PROSIMA with knowledge of PROSIMA's high failure rate and increased risk for complications.

On January 3, 2012, following numerous reports of serious mesh-related complications associated with vaginally placed synthetic mesh kits, like the PROSIMA, the FDA issued a 522 order requiring Ethicon to conduct a Post-Marketing Surveillance study to demonstrate the safety and efficacy of its transvaginal mesh kits, including the PROSIMA. [60] The FDA pointed out that it was concerned that the published literature indicated a lack of added clinical benefit compared to non-mesh repair.[61]

On February 1, 2012, Ethicon responded by providing the FDA with its Postmarketing Surveillance Plan (PS 12004).[62] On April 2, 2012, the FDA informed Ethicon that its plan was insufficient to demonstrate safety and efficacy of PROSIMA and Ethicon's plan was rejected**.** On May 9, 2012, Ethicon notified the FDA that rather than conduct studies to demonstrate the safety and efficacy of PROSIMA, Ethicon would withdraw PROSIMA from the market if the FDA would agree not to require Ethicon to

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[59] ETH.MESH.03162936
[60] ETH.MESH.08565137
[61] ETH.MESH.02658539
[62] ETH.MESH.07724636

conduct safety and efficacy studies.[63] Ethicon's own Key Opinions Leader Vincent Lucente informed Ethicon that he was displeased with PROSIMA which he described to Ethicon's employee Rosalyn Harcourt as "a reckless product."[64] Dr. Lucente's sentiments were shared by other Ethicon KOLs as well.[65,66,67,68,69,70] Andy Meek, Ethicon's U.S. Professional Education Manager, detailed these concerns from Ethicon's KOLs in an email to himself dated February 10, 2009 wherein outlines the feedback that he received from several KOLs who described PROSIMA as a "'Big mistake', 'Don't do it', 'Give me the VSD and keep PROSIMA.'"

Ethicon's internal documents demonstrate that Ethicon rushed the PROSIMA to market in the face of overwhelming evidence that PROSIMA would cause an unacceptably high rate of life-altering complications with no benefit over traditional methods for treating pelvic organ prolapse.[71,72,73,74,75,76,77,78] Despite the significant safety and efficacy problems with PROSIMA, Ethicon pushed the product onto the market quickly generating significant revenues. In an email dated April 19, 2010, Kevin Frost, Ethicon's PROSIMA Product Director, congratulated his colleagues: "**We have hit a very significant milestone with**

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[63] ETH.MESH.05600776
[64] ETH.MESH.05009194
[65] ETH.MESH.00057757
[66] ETH.MESH.02156725
[67] ETH.MESH.02156730
[68] ETH.MESH.00281482
[69] ETH.MESH.01186129
[70] ETH.MESH.00548923
[71] ETH.MESH.08966061
[72] ETH.MESH.07378350
[73] ETH.MESH.00794750
[74] ETH.MESH.00548923
[75] ETH.MESH.03686819
[76] ETH.MESH.00281482
[77] ETH.MESH.03162936
[78] ETH.MESH.05009194

the Prosima launch, $1 million dollars in salese! This makes Prosima one of the fastest launches ever, in the mesh kit market!" [79,80]

Internal Ethicon documents demonstrate that Ethicon was aware that PROSIMA and PROLIFT were defectively designed and placed patients at an unacceptable risk of suffering serious complications. For example, in Ethicon's August 27, 2007 project plan for Project Lightening, Ethicon discussed a need for a lightweight, large pore mesh to replace the defectively designed products currently on the market. Ethicon's document acknowledges the unacceptable risks associated with products like the PROLIFT and PROSIMA and the need for a safer alternative design using Ethicon's lightweight, large pore ULTRAPRO to treat pelvic floor prolapse which would:

> Reduce[] sexual dysfunction issues with current meshes: Minimize vaginal stiffness (shrinkage,) (sic) dyspareunia and permanent pain.
>
> Lower the rate of recurrence due to tissue contraction.
>
> Minimize exposure

THE CLINICAL PATH AND DATA

To date, there is no published randomized clinical trial on PROSIMA. Hence, there is no published RCT comparing PROSIMA to native tissue repair or other mesh repairs.

7/03/2004 Case Series of "Y" and "Cross" Mesh

On **July 3rd of 2004,** Dr. Carey's patent application was published.[81] In this application Dr. Carey describes a case series that included 49 women who underwent implantation of "Y" and "Cross" shaped mesh in the anterior and posterior vagina

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[79] ETH.MESH.00794750 (emphasis in original).
[80] See also ETH.MESH.03686819
[81] WO2004045457 A1

compartments (Figure 1). Dr. Carey states that his invented method was used for this case series. Accordingly, the anterior and posterior native tissue would have been plicated and the mesh would have been secured to the fascia with sutures.

Findings: 49 Patients observed for a total of 4 wks had no prolapse into the distal half of vagina at 4 weeks.

Issues:

- Patients only followed for 4 weeks
- Observational data with no control group
- No report of pre-operated prolapse stage
- In accordance with invented method
    - Native tissue plicated beneath the mesh
    - Mesh was sutured to fascia
- No balloon associated with splint (not c/w invention)
- Patients not seen until 4 weeks post op (gauze pad unlikely)
- No report of complications or other adverse events.

Summary: A small group of women with an unknown degree of prolapse underwent implantation of two mesh shapes in accordance with the invented method of Dr. Carey. The anterior shape used for combined cases, a cross, was not used for PROSIMA. A splint was used for 4 weeks. No balloon was used. At 4 weeks following transvaginal implantation of an unknown mesh type, with one shape differing than the PROSIMA shape, who underwent concomitant native tissue repair, followed by use of a VSD not associated with a balloon, 49 women with an unknown degree of prolapse did not have prolapse to the distal half of the vagina. There was no control group. There is no ability to determine if any

of the described benefit is from the native tissue repair or the mesh. There is no ability to determine if any benefit is less than, equal to or more than that with native tissue repair alone or other prolapse surgeries.

Higgs, PJ; Carey, MP; Cornish, A; Slack, M., SURGERY FOR PELVIC ORGAN PROLAPSE USING MESH AND A NEW VAGINAL SUPPORT DEVICE: A 6 MONTH FOLLOW UP. Int Urogynecol J (2006) 17 (Suppl. 2):S101–S152

In **September of 2006**, Higgs and Carey presented six month follow-up observations of 69 women with stage 2 or greater pelvic organ prolapse who underwent implantation with Gynemesh PS. A "Y" shaped mesh was used for the posterior repairs and a "Cross" shaped mesh was used for the anterior repairs (Figure 2). Minimal details were provided in this abstract. However, further details were disclosed in the 2007 publication of the one-year continuation of this observational report and incorporated herein. The native tissue, fascia, was plicated beneath the mesh. The arms of the cross mesh were not placed in tunnels to the origin of the ATFP but taken laterally to the adjacent ATFP.A vaginal stent was placed for 4 weeks following the surgery. No balloon was placed. Success was defined as POP of stage 0 or 1. Subjective effects were evaluated by validated QOL questionnaires.

Findings:

- 96% of 69 women had success at 6 months (POP-Q stage 0 or 1)
- 73% satisfaction
- 12% with sexual problems.

Issues:

- Patients only followed for 6 months
- Observational data only with no control group

- In accordance with invented method, Native tissue was plicated beneath mesh.
- No balloon was associated with the splint (VSD)
- At the time of this publication, Dr. Carey had already signed a deal with Ethicon that paid $100,000 for the publication of his data in a peer reviewed journal, provide $1,000,000 to Dr. Carey upon commercialization of PROSIMA, and could provide over $6,000,000 per year to Dr. Carey based upon worldwide sales of PROSIMA. This is very strong incentive for the publication of data supportive of PROSIMA.

Summary: A small group of women with stage 2 or greater POP-Q POP underwent implantation of Gynemesh PS mesh shapes in accordance with the invented method of Dr. Carey. The anterior shape, a cross, and the method of inserting such was not used for PROSIMA. A splint was used for 4 weeks. No balloon was used. At 6 months following transvaginal implantation of Gynemesh PS, with one shape and implantation method differing than the PROSIMA shape and method, with concomitant native tissue repair, followed by use of a VSD for 4 weeks not associated with a balloon, 96% of women had less than stage 2 POP. There was no control group. There is no ability to determine if any of the described benefit is from the native tissue repair or the mesh. There is no ability to determine if any benefit is less than, equal to or more than that with native tissue repair alone or other prolapse surgeries. A lead investigator was the financially incentivized inventor of the PROSIMA method and at least one other author was a paid consultant of Ethicon.

Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397

In **February of 2007**, Dr. Carey, Dr Slick, and co-investigators reported 1 year follow-up of their 2006 observational study. Ninety-Five women operated on between June of 2004 and February of 2005 were included. This publication provided more descriptive information including drawings. The anterior method was different that the PROSIMA method in several ways. The anterior mesh was a different shape than the PROSIMA mesh and, unlike the PROSIMA method, did not spare the distal 1/3rd of the vagina (Figure 3).[82] The anterior method for patients with apical failure also differed than the PROSIMA method. The authors used a Y" shaped mesh. However, rather than carrey the mesh back along the ATFP to the origin of the ATFP, the arms were place "onto the sacrospinous ligaments". All patients received pre-operative I.V. antibiotics, 48 hours of post-operative antibiotics, and then 5 days of oral antibiotics. This differs than the PROSIMA method that only teaches optional antibiotics.

Findings:

- 13% of the 80 women available for 12 month f/u failed
- 28% of the 96 women failed if those lost to follow-up failed
- 13% reported subjective failure (to pressure symptoms)
- 33% de novo POP of untreated posterior compartment
- 22% de novo POP of untreated anterior compartment
- 33% subjective failure by predetermined VAS cut off

[82] Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397. The anterior mesh was carried all the way up to "the pubic bone" and, as seen in Figure 2, the mesh continues the full length of the vaginal all the way to the external uethral meatus..

- 23% slippage or protrusion of the sutured VSD
- 4% mesh extrusion
- 2% de novo SUI

Issues:

- Patients only followed for 12 months
- Observational data only with no control group
- The anterior methods are different than PROSIMA.
    - The mesh was not restricted to the proximal 2/3rd of the vagina.
    - For anterior compartment surgery, a "Cross" shape was used and not a "Y" and such shape did not contact the majority of the ATFP
    - For anterior compartment surgery associated with apical failure, the "Y" mesh was not carried to the origin of the ATFP, but was carried back to a more cephalad and dorsal position, the sacrospinous ligaments.
- No tracking of de novo dyspareunia. Therefore do not know how much treatable dyspareunia was exchanged for difficult to treat or untreatable dyspareunia.
- Vaginal discharge data is not collected (incidence, severity, bother). We do not no the incidence and severity of the adverse event.
- Although only a 4% incidence of mesh extrusion is reported, a unique 2 layered non interlocking everting mucosal closure technique was used. Indeed, the authors opine that the low extrusion rate is possibly a result of the technique and not PROSIMA device. Additionally, the 2-3 year f/u of these patients found a 10% extrusion rate.[83]

[83] T. Sayer & J. Lim & J. M. Gauld & P. Hinoul & P. Jones & N. Franco & D. Van Drie & M. Slack & for the Prosima Study Investigators. Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J (2012) 23:487–493. See Table that shows 11/110 pts with extrusion.

- Although only 2% de-novo SUI, the authors to not correct for the 34% of patients that underwent concomitant sling procedures that may have represented as many as 50% of those undergoing anterior PROSIMA implants. Authors also do not correct for the 13% of patients that had prior incontinence surgery. The data on de-novo SUI is not valid unless qualified by or corrected for the up to 50% of women that had concomitant slings and previous incontinence surgery.
- In accordance with invented method, Native tissue was plicated beneath mesh.
- No balloon was associated with the splint (VSD)
- At the time of this publication, Dr. Carey had already signed a deal with Ethicon that paid $100,000 for the publication of his data in a peer reviewed journal, provide $1,000,000 to Dr. Carey upon commercialization of PROSIMA, and could provide over $6,000,000 per year to Dr. Carey based upon worldwide sales of PROSIMA. This is very strong incentive for the publication of data supportive of PROSIMA.

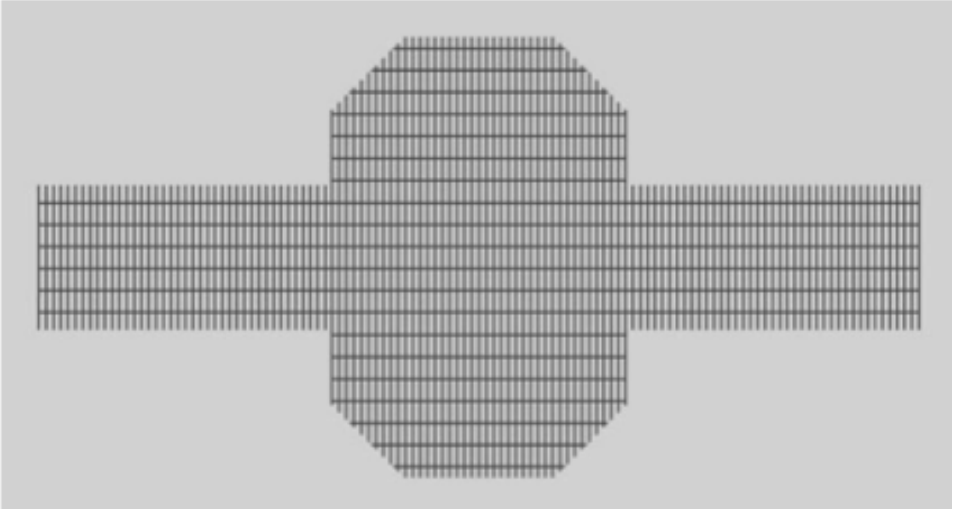

FIGURE 2

CROSS SHAPED MESH USED BY CAREY ET AL

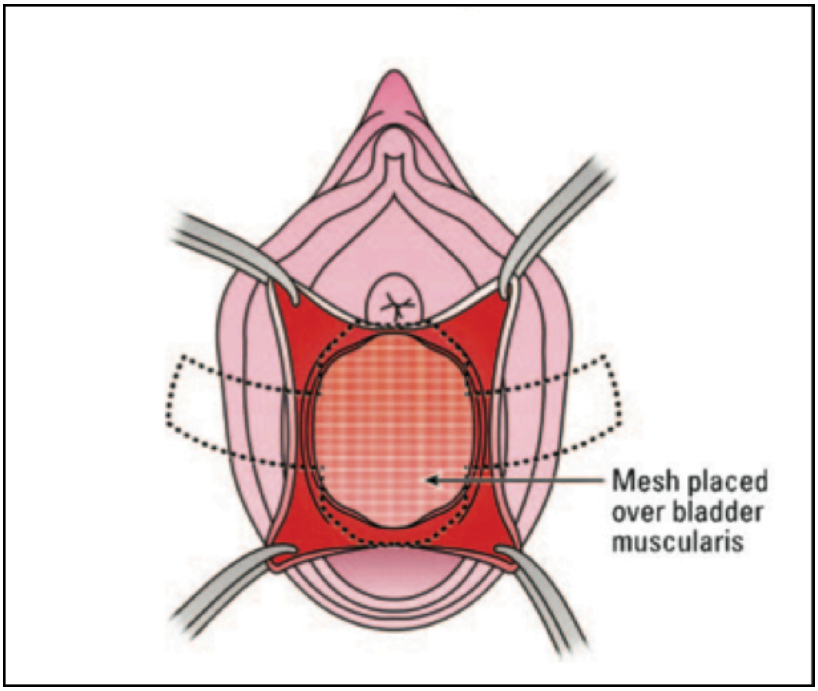

FIGURE 3

ANTERIOR MESH CAREY ET AL

Summary: A small group of women with stage 2 or greater POP-Q POP underwent implantation of Gynemesh PS mesh shapes in accordance with the invented method of Dr. Carey. As this is an extension of the 2006 study, it carries forward all of the same weaknesses and concerns. Putting such concerns and weaknesses aside, at most, this study can be considered a pilot, uncontrolled, observational study that suggests that the a no-balloon modification of the method of Dr. Carey, a method with multiple distinctions from both the PROSIMA METHOD and PROSIMA instructions, may be as efficacious as native tissue prolapse surgery at one year.

Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG 2009;116:1380–1386.

In **July of 2009,** Dr. Carey and his co-investigators reported on the one year follow-up of 139 women randomized to either a modified version of the patented Carey method (69 patients) or native tissue repair (70 patients). Women with stage two or greater POP were randomized to either combined anterior and posterior mesh over a plication (native tissue repair) or combined anterior and posterior plication (native tissue repairs). The investigators once again used the "Cross" shaped mesh for the anterior compartment surgery and tunneled this mesh laterally to the ATFP. The anterior mesh was not tunneled to the ATFP (The PROSIMA anterior mesh would be different; a "Y" shape, and be implanted differently, tunneled to the origin of the ATFP). Consistent with the previous publications, the patients being implanted with mesh all received the Carey antibiotic protocol, I.V. antibiotics pre-operatively, 48 hours of I.V. antibiotics post-operatively, and an additional five days of oral antibiotics. The native tissue group only received pre-

operative antibiotics. The mesh implantation method deviated from the method Dr. Carey described in his patent application, the method of utilized in his two previously published observational studies, and the method taught for the PROSIMA devise; No VSD was utilized. Success was once again defined as POP-Q of less than stage 2 at one year.

Findings:

- No significant difference in anatomic success between the groups
- No significant difference in subjective outcomes between the groups.
- 5.6% extrusion rate (75% excised)
- De novo dyspareunia rate: 16.7% in mesh group and 15.2% in native tissue group.

Issues:

- Patients only followed for 12 months
- The mesh group was actually a mesh plus native tissue group. Hence the findings of the study are comparing mesh plus native tissue to native tissue alone.
- Approximately half of the patients in each group underwent concomitant native tissue colpopexy (SSLF) and this was not corrected for. Hence, all conclusions regarding efficacy of mesh vs. native tissue repair are tenuous and no valid conclusions can be drawn without correction for SSLF (Those with and without SSLF would need to be analyzed separately).
- No VSD was utilized. Hence, even after correction for SSLF, none of the findings could be extended to the PROSIMA device.
- The anterior method and shape is different from the PROSIMA method and shape. Hence, even if it was revealed that a VSD with balloon was used for 3-4 weeks and

the data was corrected for SSLF, none of the findings could be extended to the anterior PROSIMA procedure.

- No subjects underwent single compartment repair. Hence, even if it was revealed that a VSD with balloon was used for 3-4 weeks and the data was corrected for SSLF, none of the findings could be extended to anterior or posterior PROSIMA and, as the anterior method and mesh shape were different from PROSIMA, none of the finding could be extended to combined anterior and posterior PROSIMA.
- Examiners were not blinded ("examiners attempted to remain blinded")
- The study was paid for by Ethicon
- At the time of this publication, Dr. Carey had already signed a deal with Ethicon that paid $100,000 for the publication of his data in a peer reviewed journal, provide $1,000,000 to Dr. Carey upon commercialization of PROSIMA, and could provide over $6,000,000 per year to Dr. Carey based upon worldwide sales of PROSIMA. This is very strong incentive for the publication of data supportive of PROSIMA.

Summary: This is a small randomized, controlled, non-blinded study, performed by a financially incentivized investigator, sponsored by the manufacturer of PROSIMA, that randomized patients to either a method of combined anterior and posterior mesh implantation that differed from both the methods previously published by Dr. Carey and the PROSIMA or native tissue repair. The investigators were on able to show a significant difference in either subjective or objective outcomes. The results of the study are tenuous at best as approximately 50% of patients underwent concomitant SSLF and the study analysis did not correct for this. Furthermore, even if such correction was to be performed now, the

findings could not be extended to PROSIMA as a neither a vaginal splint or VSD with balloon were used and, in addition, the mesh group all underwent an anterior implant different than PROSIMA. Addressing the findings of the study without reference to the above noted issues, the authors concluded, "In this study, vaginal surgery augmented by mesh did not result in significantly less recurrent prolapse than traditional colporrhaphy 12 months following surgery". "A larger study is required to more conclusively assess the effectiveness and safety of mesh-augmented vaginal repair surgery". Although Ethicon sponsored this study, I can find no evidence that Ethicon sponsored and completed this larger randomized controlled trial recommended by the author, the inventor of the PROSIMA method.

Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.

In **October of 2009,** Zyczynski, Carey and other investigators reported their one year observations on patients undergoing surgery with PROSIMA. One hundred and thirty women with POP-Q stage 2 and 3 POP underwent surgery with the PROSIMA device at one of 11 sites. The PROSIMA was implanted with a method in accordance with the PROSIMA IFU (The IFU teaches plication as optional. Patients in this study were plicated). Anatomic success was defined as POP-Q of less than stage 2. The authors cited the Ethicon rat study previously discussed herein as justification for removal of the VSD at 3-4 weeks, "The recommended duration of VSD wear (3-4 weeks after surgery) is supported by preclinical testing that established that polypropylene mesh reaches a steady-state of tissue integration at 28 days." The authors also cite, in support of a 3-4 week removal of the VSD,

a rat study in which Gynemesh was implanted in the subcutaneous tissues of the rat back.[84] The mesh was pulled through the rat skin incision and left exteriorized (Figure 4). Tension was applied horizontally at different points in time. This study found that horizontal pull-out forces for mesh in a rat back plateau at 25 days.

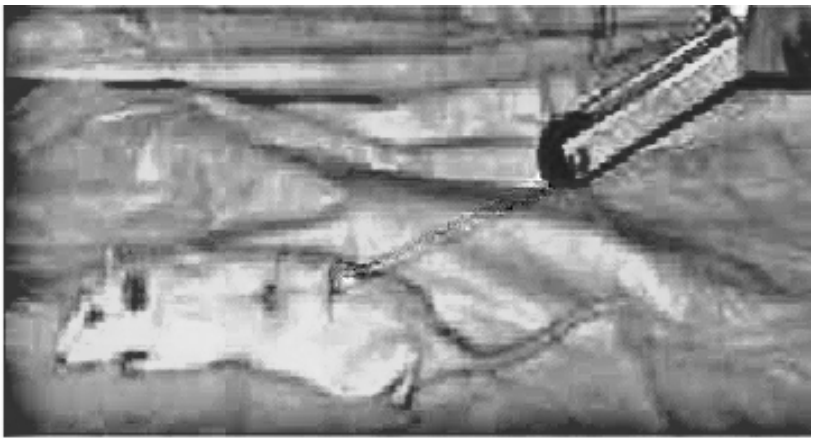

FIGURE 4

Mesh through the skin of rat.[85]

Findings:

- 77% anatomic success at one year
- 87% anatomic success if changed definition of success to prolapse above hymenal ring.
- 57% anatomic success for those patients undergoing only anterior PROSIMA
- 73% subjectively much better
- 8% mesh extrusion. 2/3rd excised.
- 82% of patients point C descends 2 cm or less

[84] Boukerrou M, Rubod C, Debet B, Boodhum R, Nayama M, Cosson M. Tissue re- sistance of the tension-free procedure: what about healing? Int Urogynecol J 2008;19: 397-400.
[85] Boukerrou M, Rubod C, Debet B, Boodhum R, Nayama M, Cosson M. Tissue re- sistance of the tension-free procedure: what about healing? Int Urogynecol J. Screen shot. Sharpening filter. 2008;19: 397-400. Figure 2.

- "Apical support 1 year after surgery was improved from baseline by 2 cm, with a mean for point C of – 6 cm".
- Failure to maintain the VSD for 21 days was associated with a higher anatomic failure rate.
- Subjective improvement noted.
- Study was failed to show success by pre-determined primary end-point of CI <20% failure.[86]

Issues:

- The reported anatomic success is not superior to native tissue repairs.
- The anatomic failure in the anterior compartment is higher than that reported in many studies on native tissue repair.
- The high anatomic failure rate of 57% for anterior mesh did not include untreated compartment failure. Studies by paid industry consultants which have looked at untreated compartment failure following anterior mesh implantation found rates ranging from 20-40 and, 2-4 x that associated with native tissue repair.[87] Correcting the failure rate of this study for the untreated compartment would need to take into consideration that 53% of patients underwent combined anterior and posterior PROSIMA leaving, according to the IFU which teaches that PROSIMA provides level one support, no untreated compartment.

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[86] ETH.MESH.01032152

[87] Vollebregt, A., Fischer, K., Gietelink, D. and van der Vaart, C. (2011), Primary surgical repair of anterior vaginal prolapse: a randomised trial comparing anatomical and functional outcome between anterior colporrhaphy and trocar-guided transobturator anterior mesh. BJOG: An International Journal of Obstetrics & Gynaecology, 118: 1518– 1527. doi: 10.1111/j.1471-0528.2011.03082.x, Withagen MI, Vierhout ME, Milani AL. Does trocar-guided tension-free vaginal mesh (Prolift) repair provoke prolapse of the unaffected compartments? Int Urogynecol J Pelvic Floor Dysfunct 2010;21:271–8.

- The overall anatomic success rate of 77% not only biased upward by the exclusion of untreated compartment failure, the success rate describes anatomic success at one year for patients undergoing a combined native tissue repair and mesh implantation. As noted earlier, the native tissue was plicated beneath the mesh.
- Mesh extrusion rate higher than reported in previous studies that did not utilize the balloon.
- This mesh extrusion rate is being reported at one year and we know that the extrusion rate increases with time. Nieminen et al, in their RCT using a similar method to that of PROSIMA but without a VSD, noted a more than doubling of the mesh extrusion rate between one and three years. Indeed, the 2 plus year follow-up of this study demonstrates an approximate doubling of the mesh extrusion rate.
- If utilized the more liberal definition of success, many patients that were with stage 2 prolapse both before and after the surgery would be considered a success.
- The mobility of point C has never been shown to be associated with symptoms of POP. Mobility of 2 cm or less has never been validated as a predictor of recurrence or a measure of success. The significance of this finding is unknown.
- Although internal Ethicon documents will site this study to as evidence that PROSIMA provides apical support, the mean improvement in point C from -4 to -6 cm has never been shown to be of clinical significance and does not represent any change in POP-Q staging.[88] It is also important to note that this 2 cm improvement was only noted in patients who underwent combined anterior and posterior PROSIMA. The only finding with regard to the effect of PROSIMA at vaginal apex is that patients with stage one apical failure treated with combined anterior and

[88] ETH.MESH.08979440

posterior PROSIMA had not progressed to Stage 2 at the one year follow-up appointment. Furthermore, point D documentation in patients with uterus in situ is conspicuously absent.

- Nieminen at all reported 87% efficacy at 3 years without suturing the mesh or using a VSD.[89] Nieminen also plicated beneath the mesh, as was taught by Carey, as was performed in all published studies including this one, and as was taught to be optional in the PROSIMA IFU.
- The authors incorrectly cite the Ethicon rat study in support of VSD removal at 3-4 weeks. As discussed previously herein, the Ethicon rat study in no way supports removal of the VSD at 3-4 weeks. Conversely, it supports maintenance of the VSD for the full 12 weeks provided by its claimed predicate device, the Silimed Vaginal Splint.
- The cited rat study does not validate VSD removal at 3-4 weeks. The mesh was pulled exteriorized (pulled through the skin). Therefore, healing skin wound confounds any measurement of pull-out resistance. Furthermore, secondary to the 90 degree angle created by the exit of the implant through the skin wound, horizontal traction is substantially absorbed by the skin. Additionally, even an accurate measure of horizontal pull-out force would not provide valuable information regarding the clinically relevant forces applied to a healing pelvic organ support mesh, as this mesh is exposed to predominantly angular (perpendicular and

[89] Nieminen, Kari, Reijo Hiltunen, Teuvo Takala, Eila Heiskanen, Mauri Merikari, Kirsti Niemi, and Pentti K. Heinonen. "Outcomes after Anterior Vaginal Wall Repair with Mesh: A Randomized, Controlled Trial with a 3 Year Follow-up." American Journal of Obstetrics and Gynecology 203.3 (2010): pg e1-8..
Kari Nieminen & Reijo Hiltunen & Eila Heiskanen & Teuvo Takala & Kirsti Niemi & Mauri Merikari & Pentti K. Heinonen. Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh. Int Urogynecol J (2008) 19:1611–1616.

not horizontal forces). It is also important to note the authors concluded that, with regard forces stabilizing at 25 days, "This schedule cannot be directly extrapolated to humans" and, discussing problems with the study device, "For these reasons, there must be some doubt regarding the real values or even the existence of the resistance plateau". In closing, the authors concluded "We will have to carry out further research to find out whether the model can be transposed to human".

- The authors noted a significant trend with regard to VSD insertion time. Increased length of insertion (beyond 21 days) was associated with higher anatomic success rates. This validates the FDA's concerns regarding removal of the VSD at only 3-4 week whereas the predicate vaginal stent was to be left inserted for 12 weeks.
- The authors state "We did not access for the presence of vaginal banding." This is a known and severe complication of armed mesh kits. In this first and only study of the PROSIMA kit, a kit without arms, the investigators have failed to access this important metric and state "Future studies should consider evaluating this known, unintended consequence of long-armed fixation meshes and its correlation to sexual function and dyspareunia."
- Although conflicts of interest were not disclosed, two authors, Gauld and Robinson, were Ethicon Employees and Slack and Carey were both paid consultants of Ethicon. The multi-million dollar financial incentive to Dr. Carey has been previously described in this report. Additionally, the "Data were maintained and analyzed by the research team of the manufacturer."

Summary: This non-randomized non-controlled observational study, funded by Ethicon and conducted by its paid consultant and direct employees, represents the first published report utilizing the PROSIMA device and method. Although the study was published in 2010, over 3 years after PROSIMA was cleared for marketing in the United States, the data was available to Ethicon by early 2009, prior to any substantial sales of PROSIMA.[90] The study reported overall anatomic success rates equal to those reported elsewhere for native tissue repairs. However, the reported success rate for the Anterior PROSIMA was concernedly lower than many reports on native tissue anterior compartment repairs.

Additionally, the authors chose not to report or consider failures in the untreated compartments, a risk uniquely high with mesh implantation surgery. Taking this into consideration, the rate of surgical failure at one year for anterior PROSIMA should be considered to be lower than that of native tissue repairs. No evidence was provided to support the efficacy of PROSIMA in the treatment of apical pelvic organ prolapse. This study reported lower efficacy and higher complications than earlier studies that excluded either used no VSD or used a VSD without a balloon. The investigators acknowledge that the efficacy was less than that previously reported for the "prototype surgery" of the inventor and is his coworkers. Based on these findings, it is hard to justify the use of the VSD with balloon and the change of the anterior mesh shape from that used in earlier studies. At a minimum, based on these findings, a randomized controlled trial comparing

[90] M. Slack, H. M. Zyczynski , C. Reisenauer , S. Khandwala , D. Van Drie , N. Franco, T. R. Sayer , C. Goepel, M. Murphy, J. Gauld, A. R. Smith, M. P. Carey; A New Operation For Vaginal Prolapse Repair Using Mesh And A Vaginal Support Device: 1 Year Anatomic And Functional Results Of An International, Multicentre Study. Int Urogynecol J (2009) 20 (Suppl 2):S157–S158. And ETH.MESH.07724646. Ethicon's response to the 522 order. Only 70 units were sold in 2009.

the PROSIMA device and method to the "Prototype Surgery" (VSD without a balloon and no VSD) should have been initiated. It was not.

In addition, the authors not only cite non-supporting literature with regard to removing the VSD at 3-4 weeks, but also find a significant association between increased insertion time and improved anatomic success. At a minimum, a randomized controlled trial to evaluate the effects of prolonged and shortened VSD insertion time should have been initiated. It was not.

With regard to the improvement in symptoms reported following PROSIMA implantation, the authors point out "We are unable to determine the contributing impact of mesh on this substantial reduction in symptoms in this cohort study. A randomized trial of colporrhaphy vs. mesh repair could contribute to the evidence-based risk/benefit analysis of augmented repairs." This study was not done.

The authors also concede that they failed to access the proposed benefit of PROSIMA over armed mesh kits, arm related sexual dysfunction and dyspareunia. The authors state that future studies should evaluate this issue. No such study was done.

Moreover, this study was done in accordance with the teachings of Carey and in accordance with the "Prototype Surgery" and, therefore, included native tissue plication beneath the mesh. Thus, any significant findings can only be claimed for PROSIMA device implantation combined with native tissue repair.

Finally, the study failed to demonstrate success of PROSIMA by its predetermined primary endpoint, confidence interval not < than 20%.

T. Sayer & J. Lim & J. M. Gauld & P. Hinoul & P. Jones & N. Franco & D. Van Drie & M. Slack & for the Prosima Study Investigators. Medium-term clinical outcomes

following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J (2012) 23:487–493

In November of 2011, Sayer and six other investigators reported the 24-34 month follow-up of patients that had been included in the 2010 Ethicon PROSIMA study (Zyczynski et al). The median follow-up time was reported to be 29 months. This was an Ethicon sponsored observational continuation study in which five of the seven authors were paid Ethicon consultants and two were Ethicon Employees. One hundred and ten women from the original study were re-consented for the extension study.

Findings:

- 69% Success rate at median of 29 months
- 84% of patients point C descends 2 cm or less
- 10% Mesh extrusion.[91]
- 73% were excised.
- 5% de novo SUI
- 5% de novo dyspareunia
- Subjective improvement noted

Issues

- Anatomic success rates dropped below the native tissue success rates reported in many studies. Although the one-year data was very concerning for Anterior PROSIMA performing less well than native tissue repairs, this 2-3 year follow-up failed to report on efficacy by compartment.

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[91] T. Sayer & J. Lim & J. M. Gauld & P. Hinoul & P. Jones & N. Franco & D. Van Drie & M. Slack & for the Prosima Study Investigators. Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J (2012) 23:487–493. See Table that shows 11/110 pts with extrusion.

- 20% of the original study group was not consented for this extension study. The anatomic success rate is most likely lower than the reported 69%.
- Untreated compartment failures were not considered anatomic failures. Based on the already described high incidence of untreated compartment failure associated with vaginal mesh implantation, if such failures were included in the study calculations, anatomic success of PROSIMA would have been further decreased. Such decrease would likely represent an efficacy well below that of native tissue repair.
- As noted in the previous discussion of the one year data, native tissue plication was performed beneath the mesh.
- Whereas the one year Ethicon study by Zyczynski et al described stability of point C (but did not show significant improvement in apical support), this 2-3 year follow-up study chose to exclude the POP-Q data on point C and provided only the mobility of point C. This omission is suspect and suggests that this measurement was excluded secondary to progression of point C (a failure of PROSIMA to treat apical failure).
- At 10% incidence of mesh extrusion, this non-randomized, non-controlled, manufacturer-sponsored study performed by Ethicon employees and paid consultants provides no meaningful evidence to suggest the PROSIMA device is associated with greater or lower mesh extrusion rates than armed mesh kits.
- Although a de novo dyspareunia rate of 5% is less than that reported for both armed mesh and native tissue prolapse surgery, it is unclear if the low reported rate is secondary to less ambitious native tissue repair performed underneath the mesh, the

limitation of the mesh to the proximal 2/3rd of the vaginal vault, or secondary to the no-armed PROSIMA method. The 5% incidence of dyspareunia must also be considered with reservation, as the inventor of the PROSIMA method, Dr. Carey, published his RCT of his no-arm mesh method (without a VSD) vs. Native tissue, and found a 17% incidence of de novo dyspareunia associated in the no-arm mesh group.

- Any subjective improvement may be secondary to the underlying native tissue repair, the mesh, or a combination of the two. Even if the investigators controlled for plication, as the original investigators pointed out "We are unable to determine the contributing impact of mesh on this substantial reduction in symptoms in this cohort study. A randomized trial of colporrhaphy vs mesh repair could contribute to the evidence-based risk/benefit analysis of augmented repairs."
- The authors do not report the mean follow-up time. The authors opted to report a median. As a longer follow-up would be more meaningful, one would expect the authors to have reported a mean that was greater than the median. Hence, it is likely that the mean follow-up is less than the reported 29-month median.
- Although the authors report a 5% incidence of de novo stress urinary incontinence, a number that is lower than that reported for other mesh kits, the authors do not correct for the fact that 52% of the anterior PROSIMA patients underwent concomitant mid-urethral sling procedures (33% of all cases had a concomitant sling procedure). Correction for concomitant sling procedures would be expected to raise the reported incidence of de novo SUI.
- 7/7 of the authors were paid by Ethicon. Two of the seven were Ethicon employees.

Summary:

This non-randomized non-controlled observational study, funded by Ethicon and conducted by its paid consultants direct employees, represents the first published report utilizing the PROSIMA device and method. This is an extension of the one-year Ethicon study reported by Zyczynski in. It is therefore subject to the same flaws and concerns previously described. Although the mean follow-up time is not disclosed, it is expected to be closer to two years than 3 years. As may have been predicted by previous RCTs on transvaginal mesh surgery, failures and mesh extrusions increased with time. Critical evaluation of the data suggests that, somewhere between 2 and 2.5 yrs, efficacy had fallen below that of traditional native tissue prolapse repairs and mesh extrusion had doubled. Of additional concern is the fact that success at 2 to 2.5 years in this uncontrolled observational study had dropped well below the success rate reported in the 3-year RCT of Nieminen et al, a study that used a similar method but no VSD.

Reports of a low incidence of de-novo dyspareunia must be considered with caution as previous data reported in a prospective RCT by the inventor of the method disclosed a incidence more than triple of that reported here. Although the incidence of mesh erosion was not higher than that reported in RCTs of vaginal mesh kits, all patients received 7 days of antibiotics (and 48 hours of I.V. antibiotics post-op) and a unique two layer mattress closure of the vaginal mucosa. As there were no control group and these measures were universally applied, these confounding variables cannot be corrected. The only conclusions that can be drawn with regard to the incidence of PROSIMA related mesh extrusion is that the implantation of the PROSIMA device with a novel double mucosal closure technique

and a novel and extended antibiotic regimen (not taught in the PROSIMA IFU) was associated with a mesh extrusion rate not greater than previously reported for transvaginal mesh surgery. As more than half of the anterior PROSIMA patients and one third of all PROSIMA patients underwent concomitant sling procedures and no statistical correction was attempted, no conclusions may be drawn with regard to the incidence of de novo stress urinary incontinence.

Any attempts to claim improved efficacy or decreased complication rates based on future statistical correction for the confounding factors of concomitant sling surgery and untreated compartment failure would only provide evidence regarding the combination of the PROSIMA device with native tissue plication. As all patients were plicated, this confounding variable cannot be corrected. Meaningful data on the efficacy and complications of the PROSIMA device itself could only be collected in a RCT that included a PROSIMA arm without concomitant plication. This study was never done.

On **April 12th of 2008**, the inventor of the PROSIMA procedure, Dr. Carey, sent an email to Ethicon's Worldwide Marketing Director and Worldwide Medical Director, Jonathan Meek and David Robinson, MD, as well as Ethicon's clinical director in Scotland, Judith Gauld and World Wide Group Marketing Director, Harel Gadot in which he declared "the clinical data need to demonstrate that PROSIMA is better than colporrhaphy and hopefully approaches the success rates for the "gold standard" procedure, abdominal sacral colpopexy."[92] He goes on to explain that these benchmarks need to be established from RCTs and quality prolapse studies and then they can determine if PROSIMA, in their PROSIMA study, "did perform better than colporrhaphy and approached success rate of "gold standard" sacral colpopexy and were the complications acceptably low." Dr. Carey

[92] ETH.MESH.03162937

closes by stating, "Tell me what you think. I can put together a draft presentation and send it for consideration. We can then carry this approach over the US a week later."

The following day, Juidth Gauld emailed Dr. Robinson and Jonathan requesting that the three of them further discuss this prior to responding to Dr. Carey.[93] Judith Gauld stated "We did state in the protocol that the study would be considered a success if the failure rate had an upper 95% CI of less than 20% at 12months. We have already failed that. I am concerned here that this looks like a good bit of spin going on, and due to his commercial interest, this is not going to come over as objective as perhaps it should. Whilst this type of message might be great once we've identified the problems, and are presenting to preceptors, etc, I'm not sure that it would be well placed in this meeting."

Judith Gauld had pointed out to Ethicon's World Wide Marketing and Medical Directors that their study failed to demonstrate success and that any attempts to compare the non-controlled observational data from the financially incentivized inventor of the procedure to RCTs on other procedures would be poorly received in their upcoming meeting. She further points out that PROSIMA has problems. Ethicon did not yield to her concerns. Ethicon was never able to demonstrate PROSIMA success by its original definition disclosed by Judith Gault and Ethicon did not conduct RCTs with its PROSIMA device. Ethicon continued to make comparisons between its biased financially incentivized data and RCTs that did not include PROSIMA.

I was unable to find any evidence of published observational or randomized controlled studies prior October of 2010 that include the patented PROSIMA method. The research I conducted demonstrated that the only studies published were authored by the financially incentivized inventor of the PROSIMA method. These studies did not utilize

[93] ETH.MESH.03162936

the PROSIMA VSD with balloon and used a different anterior mesh shape (and method). These studies failed to demonstrate any superiority to native tissue prolapse surgeries. In 2011 the Ethicon PROSIMA 29 month median follow-up observational data was published. The patients in this study did undergo the PROSIMA method as described by the PROSIMA IFU. All patients underwent concomitant plication of native tissue (taught to be optional by the IFU) and all patients received 7 days of antibiotic therapy (taught to be optional by the IFU). This study suggested inferiority of PROSIMA to native tissue surgery, no-arm mesh surgery performed without a VSD, and existing armed mesh kits. Although the authors of the PROSIMA studies pointed out the need for randomized controlled trials to validate both safety and efficacy, these trials were never performed.

THE 522 ORDER

On **January 3 of 2012** the FDA issued Ethicon, in accordance with Section 522 of the Federal Food, Drug, and Cosmetic Act, an order for postmarket surveillance of its PROSIMA device.[94] The FDA informed Ethicon that its PROSIMA device was reasonably likely to cause "serious adverse health consequences" and "was intended to be implanted in the body for more than one year." Either of these circumstances can cause an order for postmarket surveillance. The FDA informed Ethicon that it was "concerned with the potential safety risks as evidenced by adverse events reported to the FDA and in the published literature" and, in addition, was "concerned with the published literature indicating a lack of added clinical benefit compared to non-mesh repair."

This order required Ethicon to submit its plan for postmarket surveillance that addressed a series of questions provide by the FDA. The FDA informed Ethicon that it would review their plan and responses and "determine whether the plan will result in the

[94] ETH.MESH.02658539

collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health." These questions were drafted to address specific concerns of the FDA regarding the PROSIMA device (and not general mesh related concerns). Some of these questions and Ethicon's responses are discussed below.[95]

- What are the rates associated with each of the following adverse events through 36 months post implant: mesh exposure in the vagina, mesh erosion into another organ, pelvic pain, infection (by type), de novo dyspareunia, vaginal shortening, vaginal scarring, de novo vaginal bleeding, atypical vaginal discharge, fistula formation, de novo voiding dysfunction including de novo incontinence, neuromuscular problems, revision/resurgery, recurrent prolapse? Are the rates of adverse events associated with the use of this device non-inferior to the rates seen in patients with similar surgeries who are not treated with mesh.
- Some of Ethicon's Responses:
    - **Vaginal Discharge**: 0.7%
        - Ethicon chose to use the MedDRA definition. Yet the FDA clearly asked for the rate of atypical vaginal discharge. Although Ethicon did not as the FDA for clarification of "atypical", 117 of 136 women in Ethicon's observational study (87%) noted of vaginal discharge. Ethicon did not compare this rate to the rate of native tissue surgery as requested by the FDA. Additionally, the FDA requested 36-month data. Ethicon only provided data from their 1-yr observational

[95] ETH.MESH.07724636

PROSIMA study. Their 29-month follow-up study did not report on discharge.

- **De novo SUI**: (4%)
  - Although the 1-year Ethicon PROSIMA study demonstrated 4%, the Ethicon 29 month extension of that PROSIMA trial found a 5% incidence of de novo SUI. Ethicon opted to report on the one year study even though the FDA requested 36 month data. Additionally, a mid-urethral sling accompanied more than half of all anterior PROSIMA implants and a midurethral sling accompanied 33% of all PROSIMA implants. We do not know what percentage of slings was performed without a diagnosis of SUI. Ethicon chose not to report the incidence of de novo SUI in patients not treated with a sling and in those without a previous incontinence surgery (19% had previous incontinence surgery). Hence, Ethicon reported an incidence of de novo SUI that was artificially decreased and declared that the incidence of SUI was less than that associated with other surgeries.
- **Dyspareunia**: 6.7%
  - It is unclear where this number comes from. However, in response to the FDA's request for randomized controlled prospective data comparing PROSIMA to native tissue surgery, Ethicon offered data on four RCTs it had previously sponsored. One of these studies was the above-discussed 2009 study by Dr. Carey, Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial.

Although Ethicon offered this study, they did not disclose its reported de novo dyspareunia rate of 17%. Ethicon did not provide the requested 36 month data on dyspareunia nor did it disclose that its 29 week extension study on PROSIMA reported "Due to the limited numbers of patients within this study and the lack of control, it is difficult to determine the true rate of de novo dyspareunia following this procedure."

- **Vaginal Shortening: 2.7%**
  - It is unclear where this number comes from. This number appears to be generated from a "yes" response to a question regarding vaginal capacity and stenosis. The Ethicon PROSIMA studies did demonstrate a statistically significant decrease in total vaginal length. 2.7% of the PROSIMA study population would represent 3 women. It is unlikely that vaginal shortening in 3 of 110 women could have resulted in the significant decrease in total vaginal length noted in the 29 month PROSIMA study. Ethicon did not provide the requested 36 month data and does not provide the comparison to native tissue surgery.

- Is the rate of effectiveness among women in which mesh is placed non-inferior to the rate of effectiveness among women with similar surgeries who are not exposed to mesh?
  - Ethicon states that PROSIMA is superior to native tissue repairs based on success of POP-Q less than stage 2. In support of this they offer the 77%

efficacy found in their 1 years observational study that had no control arm and offer up the control arm of three Ethicon sponsored RCTs. Only one of these cited studies used a no-armed mesh. The Dr. Carey RCT that is cited here by Ethicon found a 65% efficacy of native tissue repair and found no significant difference in objective success between the mesh and native tissue groups. Ethicon also does not offer any non-Ethicon sponsored RCTs such as the Chmielewski et al RCT that found an 89% efficacy using the hymenal ring definition of success (this definition resulted in 87% PROSIMA efficacy).[96] Ethicon also omitted to disclose that the efficacy in the anterior compartment at one year was only 57% and that their 29-month data found that the overall success rate decreased to 69%. Ethicon's claim of superiority is unsubstantiated and as note elsewhere in this report. The 29 month Ethicon data suggests inferiority. Ethicon also did not provide the requested 36 month prospective controlled data.

- In response to the FDA's request for "a randomized controlled trial or prospective cohort study design that compares your device to a control (e.g. transvaginal Urogynecology surgery without mesh) through 3 years follow-up," Ethicon did not provide a study protocol, but instead cited 4 mesh trials it had previously sponsored. None of these trials included PROSIMA and three of them used PROLIFT. Ethicon was unable to provide the requested safety and efficacy data to the FDA.

On **April 2nd of 2012** the FDA rejected Ethicon's 522 responses**.** The FDA cited numerous failures to respond to the 522 questions as well as deficiencies in the proposed study plan.

[96] Chmielewski L, Walters MD, Weber AM, Barber MD. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1–69.e8

The FDA stated "Because of this lack of information, review of the protocol cannot continue and, accordingly, we have listed the following deficiencies, which require the responses as indicated."[97] The FDA cited numerous failures to respond to the 522 questions and deficiencies in the proposed study plan.

On **May 9th of 2012** Ethicon notified the FDA that it was in receipt of the above noted letter of deficiency and that it had opted to stop commercializing PROSIMA. Ethicon requested that the FDA therefore put a hold on the 522 order.

THE PROSIMA LABELING

IFU Section: Description: In this section each component of the PROSIMA kit is described. The description of the Gynecare Gynemesh is reviewed herein.

> GYNECARE GYNEMESH PS is mesh constructed of knitted filaments of extruded polypropylene identical in composition to PROLENE Polypropylene Suture, (ETHICON, INC.). This material, when used as a suture, has been reported to be nonreactive and to retain its strength indefinitely in clinical use. The mesh affords excellent strength, durability, and surgical adaptability, with sufficient porosity for necessary tissue ingrowth. Blue PROLENE Suture monofilaments have been incorporated to produce contrast striping in the mesh. The mesh is constructed of reduced-diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50 percent more flexible than standard PROLENE Polypropylene Mesh. The mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling. The bi-directional elastic property allows adaptation to various stresses encountered in the body.

Ethicon's IFU provides false information which is inconsistent with medical and scientific literature, Ethicon's internal documents and my knowledge, training, education and experience, in the following ways:

"This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use."

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[97] **ETH.MESH.08565137**

This statement misleads surgeons to believe that the Gynemesh PS of PROSIMA is non-reactive. Not only is this not true, both the scientific and medical literature (including Ethicon's own investigation) have consistently shown that PROLENE polypropylene is reactive.[98] Ethicon was targeting low skilled surgeons and surgeons not presently using synthetic mesh.[99] This group of surgeons is an easy target for such misrepresentation, as they are not well familiarized, by experience, with the reactive and inflammatory response created by transvaginal mesh implantation. In this IFU claim Ethicon misleads the user to believe that the Gynemesh of the PROSIMA is not reactive, does not undergo in vivo degradation and retains its strength indefinitely following implantation. This statement is inconsistent with the medical and scientific literature, Ethicon's own internal studies and documents, and my knowledge, training, education and experience.[100,101,102,103,104,105,106,107,108,109,110,111]

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[98]

[99] ETH.MESH.03048943

[100] Liebert, et al., "Subcutaneous Implants of Polypropylene Filaments." *Journal of Biomedical Materials Research*, (1976) 10(6):939–951

[101] Jongebloed et al., "Mechanical and biochemical effects of man-made fibres and metals in the human eye, a SEM-study, *Documenta Ophthalmologica* (1986) 61, 303-3012

[102] Mary, et al., "Comparison of the In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery" *ASAIO Journal*, (1998) 44(3):199–206

[103] Clavé, et al., "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." *Int. Urogynecology J.*, (2010) 21(3):261–270

[104] Costello, et al., "Characterization of Heavyweight and Lightweight Poly." *J. Biomed. Mater. Res. B Appl. Biomater.*, (2007) 83B(1):44–49; Costello et al., "Materials Characterization of Explanted Polypropylene Hernia Meshes," *J. Biomed. Mater. Res. B Appl. Biomater.*, (2007) 83B(1):44–49.

[105] Wood, et al. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." *J. Mater. Sci. Mater. Med.*, (2013) 24(4):1113–1122

[106] ETH.MESH.12831405

[107] ETH.MESH.15955438

[108] ETH.MESH.15955440

[109] ETH.MESH.15955462

[110] ETH.MESH.12831391-1404

"The mesh affords excellent strength, durability, and surgical adaptability, with sufficient porosity for necessary tissue ingrowth."

This statement misleads surgeons to believe that the Gynemesh PS of PROSIMA will remain substantially unchanged after implantation and, any properties of the mesh as described in the IFU ("50% more flexible" and "elasticity in both directions") that are requisite to normal vaginal function will therefore remain after implantation. The term durable is familiar to both patients and physicians. The Merriam Webster dictionary defines "durable: able to exist for a long time without significant deterioration."[112] There is ample evidence in both the medical and scientific literature as well as Ethicon's internal documents to demonstrate that polypropylene, including PROLENE, will undergo surface degradation after implanted in the human body. It is well known that the polypropylene is attacked by the immune system resulting in oxidation and degradation with substantial loss of its original properties.[113] This is congruous with my clinical experience. I have explanted hundreds of pieces of polypropylene mesh from the vagina and all of these explants have demonstrated complete loss of flexibility and elasticity. Ethicon misleads the user to believe that the Gynemesh of the PROSIMA device provides excellent durability of critical properties.

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[111] ETH.MESH.05453719

[112] "Definition of DURABLE." Merriam Webster, n.d. Web. <http://www.merriam-webster.com/dictionary/durable>.

[113] Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res. 83B.1 (2007): 44-49.. Clavé, Arnaud, Hannah Yahi, Jean-Claude Hammou, Suzelei Montanari, Pierre Gounon, and Henri Clavé. "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." International Urogynecology Journal Int Urogynecol J 21.3 (2010): 261-70. , Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine 24.4 (2013): 1113-122.

This statement also misleads surgeons to believe that Ethicon has demonstrated that the Gynemesh PS of PROSIMA has sufficient pore size to provide for the necessary tissue ingrowth following vaginal implantation. Ethicon's own study, a study referenced in the Gynemesh PS IFU, demonstrated a concerning process in direct contradiction to the Ethicon claim of "sufficient pore size for necessary tissue ingrowth." This study found "[T]here was a reduction in cellularity in the surrounding connective tissue and a decrease in the amount of fibrosis in the mesh pores."[114] These findings of Gynemesh PS demonstrate that Gynemesh PS impairs tissue ingrowth. This finding was recently validated by Liang et al who compared the effects of GyneMesh PS to two lower weight, higher porosity, less stiff meshes following implantation into a primate vagina rather than a Rat back. This study, which was sponsored by the NIH, found "Following implantation with the heavier, less porous, and stiffer mesh, Gynemesh PS, the degradation of vaginal collagen and elastin exceeded synthesis, most likely as a result of increased activity of MMPs, resulting in a structurally compromised tissue."[115]

Well in advance of the marketing of PROSIMA, in 2007, Muhl et al reported on effective porosity, demonstrating that in order to allow tissue ingrowth and prevent the bridging fibrosis associated with mesh contraction, pore sizes should remain greater than 1000 microns under the typical loads seen following implantation.[116] In contrast to demonstrating effective porosity, Ethicon acknowledged that poor size had not been

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[114] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecol J 17.S1 (2006): 26-30.
[115] Liang, Rui, Wenjun Zong, Stacy Palcsey, Steven Abramowitch, and Pamela A. Moalli. "Impact of Prolapse Meshes on the Metabolism of Vaginal Extracellular Matrix in Rhesus Macaque." Obstetrical & Gynecological Survey 70.6 (2015): 385-87.
[116] Muhl, et al. New Objective Measurement to Characterize the Porosity of Textile Implants. J. Biomed Mater Res Part B: Appl Biomater 84B:176-183, 2008. Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia DOI 10.1007/s10029-012-0913-6.

measured during product development, "Pore size in microns was not measured during the development of the Prolene Soft Mesh. The total percent area that is open was measured and is considered an accurate method. Since the product construction results in irregular pore geometries and size, it is not accurate to report a distinct pore size."[117] Ethicon statements misleads the user to believe that the Gynemesh PS contained within the PROSIMA device provides sufficient porosity for tissue ingrowth. These finding are consistent with my experience of explanting hundreds of pieces of vaginal mesh including Gynemesh PS and consistent find that the mesh is encapsulated in a rigid scar plate and has shrunken or contracted significantly which causes severe life-altering complication that my patients experience.

The mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling. The bi-directional elastic property allows adaptation to various stresses encountered in the body."

This statement misleads surgeons to believe that the Gynemesh PS of PROSIMA will maintain bidirectional elasticity following implantation in order to provide the necessary compliance for vaginal function. Ethicon recognized the importance of such property as is disclosed in the publication of its Gynemesh PS rat study, a study cited in its IFU that "Elasticity in the range of 20–35% has been reported to match the compliance of surrounding tissues to avoid both extrusion of the material and patient discomfort."[118] As previously discussed herein, there is evidence that there is complete or nearly complete loss

[117] ETH.MESH.01431617, 6-14/15-2006, email chain about Gynemesh PS/Prolene Soft mesh pore size, Robert Rousseau: (Ethicon principal engineer)
[118] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecol J 17.S1 (2006): 26-30.

of elasticity following transvaginal implantation.[119] These finding are consistent with my experience of explanting hundreds of pieces of vaginal mesh including Gynemesh PS in which I have found no residual elasticity. In this IFU claim, Ethicon misleads the user to believe that the Gynemesh PS of PROSIMA is the world's first transvaginal mesh that not only maintains elasticity but maintains sufficient elasticity to allow for function of the vagina under normal stresses.

IFU: Section 1: Principles Of The Procedure Using The Gynecare Prosima System.

"Once inflated, the Balloon replaces traditional gauze packing by filling the vaginal cavity and abutting the Mesh Implant(s) to the vagina. The day after surgery, the Balloon is deflated and removed from the vagina without dislodging the VSD."

Unlike the VDS Balloon, a gauze pad is non-occlusive and does not create an anaerobic environment favoring the growth of anaerobic bacteria. In contrast, moist gauze pads remains a maintain in the treatment of infected wounds, the wet-to-dry dressing. The VSD balloon had replaced a non-occlusive device known to treat infections with an occlusive device known to be associated with the creation of an anaerobic environment, malodorous discharge, and ulceration.[120] Furthermore, the use of gauze for 24 hours enjoyed over a century of clinical use. Surgeons, by means of historical outcomes and personal experience, had learned that the 24-hour use of gauze packing provided a safe and

[119] Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res. 83B.1 (2007): 44-49.. Clavé, Arnaud, Hannah Yahi, Jean-Claude Hammou, Suzelei Montanari, Pierre Gounon, and Henri Clavé. "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." International Urogynecology Journal Int Urogynecol J 21.3 (2010): 261-70. , Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine 24.4 (2013): 1113-122. Dietz, Hans Peter, Max Erdmann, and Ka Lai Shek. "Mesh Contraction: Myth or Reality?" American Journal of Obstetrics and Gynecology 204.2 (2011): 173.e1-4,

[120] Magali, R, Schulz, J, Harvey, M A, Technical Update on Pessary Use. J Obstet Gynaecol Can 2013;35(7 eSuppl):S1–S11

effective method of acute post-operative hemostasis. Ethicon performed no studies, no animal studies, no observational cohort studies, and no randomized control studies to validate the replacement of gauze packing with a vaginal balloon to be removed the day after surgery. The FDA in its 2001 FDA Guidance on Medical Device patient labeling states that labeling should include "Risk Message: should acknowledge uncertainties, including lack of currently available scientific knowledge". Ethicon did not disclose to either surgeons or patients that it was uncertain as to whether or not the VSD balloon could safely and effectively replace the traditional gauze packing. Ethicon did not disclose to either surgeons or patients that there was a lack of currently available scientific knowledge to support the use of the VSD Balloon as a replacement for the traditional gauze packing.

"The VSD remains in place for a maximum of 4 weeks following surgery, during tissue ingrowth into the Mesh Implant(s)". "By reinforcing the vaginal repair with the Mesh Implant and supporting the vagina with the VSD for 3 to 4 weeks following surgery, the GYNECARE PROSIMA System is designed to reduce the risk of surgical failure and recurrent prolapse."

No pessary had ever been clinically tested for safety or efficacy as vaginal stent following the surgical implantation of a foreign body, more specifically polypropylene mesh. This is a point of concern as pessary use, not associated with surgery, has been reported to be associated with up to a 73% incidence of complications including erosions, bleeding and foul odor.[121] Other authors have reported lower but concerning rates of pessary related complications. Hanson et all reported a 9% incidence of vaginal erosions and a 2.5% incidence of infections.[122] Additionally, pessary use has been associated with a 3 fold

[121] Bai SW, Yoon BS, Kwon JY, Shin JS, Kim SK, Park KH, et al. Survey of the characteristics and satisfaction degree of the patients using a pessary. Int Urogynecol J Pelvic Floor Dysfunct 2005;16(3):182–6.
[122] Hanson LA, Schulz JA, Flood CG, Cooley B, Tam F. Vaginal pessaries in managing women with pelvic organ prolapse and urinary incontinence: patient characteristics and factors contributing to success. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(2):155–9., Abdool Z, Thakar R, Sultan AH, Oliver RS. Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2011;22(3):273–8., Lazarou G, Scotti RJ, Mikhail

increased risk of Bacterial Vaginosis (BV), a disorder known to be associated with a significantly increased risk post surgical infection.[123] Of yet further concern is that the proposed predicate device of the PROSIMA VSD, the Silimed Vaginal Stent, was neither indicated nor tested as a stent following the implantation of a foreign body (e.g. mesh).

Ethicon performed no testing to validate the safety and efficacy of the VSD for any given time period. As demonstrated in the deficiencies described herein with regard to the 522 response to the FDA, Ethicon was unable to provide the FDA with any comparative data, observational or randomized controlled, to demonstrate safety and efficacy of the PROSIMA VSD method compared to the extensively used historical methods. Ethicon did not collect any comparative data, retrospective or prospective, that demonstrated safety or efficacy of the VSD. By way of example, no study was performed in which patients were randomized to the PROSIMA method of the IFU and the PROSIMA method of the IFU without the VSD. By way of example, no study was performed in which patients were randomized to the PROSIMA method with VSD insertion for different lengths of time. Such studies were necessary to demonstrate safety, efficacy, and if safety and efficacy existed, the optimal time for VSD insertion. As described earlier herein, the FDA noted that the 3-4 week insertion time was markedly different than the insertion time taught for the claimed predicate device, the Silimed Vaginal Stent. Ethicon did not respond with any comparative data (Silimed vs VSD), but rather offered data from its study in which it

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MS, Zhou HS, Powers K. Pessary reduction and postoperative cure of retention in women with anterior vaginal wall prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2004;15(3):175–8., Magili, R, Schulz, J., Harvey, M.A., Technical Update on Pessary Use. J Obstet Gynaecol Can 2013;35(7 eSuppl):S1–S11.

[123] Soper DE, Bump RC, Hurt WG. Bacterial vaginosis and trichomoniasis vaginitis are risk factors for cuff cellulitis after abdominal hysterectomy. Am J Obstet Gynecol 1990; 163:1016–21; discussion 1021–3., Larsson PG, Carlsson B. Does pre- and postoperative metronidazole treatment lower vaginal cuff infection rate after abdominal hysterectomy among women with bacte- rial vaginosis? Infect Dis Obstet Gynecol 2002;10:133– 40., Larsson PG, Carlsson B. Does pre- and postoperative metronidazole treatment lower vaginal cuff infection rate after abdominal hysterectomy among women with bacte- rial vaginosis? Infect Dis Obstet Gynecol 2002;10:133– 40.

implanted Gynemesh PS in the subcutaneous tissue of rat backs without any VSD. This study did not support the 3-4 week VSD insertion period.

The study demonstrated that the tissue response to the Gynemesh PS continued without significant regression through the full 91 days of the study with ongoing inflammation that would bode against the addition of a secondary foreign body (VSD), and the study also provided data that demonstrated that Gynemesh PS was uniquely associated (compared to the other mesh implants of this study) with erosion down to and adherence to underlying muscle. Hence, the implantation of Gynemesh in the backs of rats did not provide any evidence in support of a 3-4 week VSD insertion. Ethicon also conducted an one year observational study and a 29 month follow up study that demonstrated a trend toward improved efficacy with longer VSD insertion times.

In conclusion, neither the Ethicon Rat or Ethicon Human studies provided validation of the 3-4 week VSD insertion time taught by the IFU, but rather raised two questions: Should the VSD be maintained for a much longer period of time as taught for its claimed predicate? Should the VSD not be used at all, as the rat study demonstrated a unique tendency of Gynemesh to erode down to and adhere to muscle, a tendency that could be accentuated by the pressure of the VSD. Interestingly, prior to commercialization of PROSIMA, there were two published RCTs performed with no-arm non-fixated methods similar to that of PROSIMA but without a stent (VSD). Both of these studies demonstrated efficacy in excess of that found in the two observational Ethicon PROSIMA studies.[124] As noted earlier, the FDA in its 2001 FDA Guidance on Medical Device patient labeling states that labeling should include "Risk Message: should acknowledge

[124] Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG 2009;116:1380–1386

uncertainties, including lack of currently available scientific knowledge". Ethicon did not disclose to either surgeons or patients that it had not demonstrated the safety or efficacy of the VSD, compared to similar surgeries not using the VSD, for 3-4 weeks or for anytime period.

Ethicon provides in its IFU that the PROSIMA with 3-4 weeks of VSD insertion is designed to reduce the risk of surgical failure and recurrent prolapse. This misleads the user to believe that PROSIMA does reduce the risk of surgical failure and recurrent prolapse and no way suggests that Ethicon designed it for this purpose but marketed it in the absence of demonstrating its ability to achieve its purpose.

IFU Section: Vaginal Incisions:

"*Incisions should be made through the full depth of the vaginal wall to reduce the potential of mesh exposure.*"

This instruction is a departure from the previous teachings of Ethicon. The Prolift Surgeons Monograph for teaches dissection through the first two of the 3 layers of the vaginal wall, placing the mesh between the fibromuscular layer and the adventitia.[125] The PROSIMA IFU here teaches a deeper implantation, an implantation through all three layers of the vaginal wall, leaving the mesh to rest directly on the bladder. As already demonstrated by the Ethicon rat study, Gynemesh PS has a unique tendency to erode deeply. Hence, PROSIMA IFU teaches a novel and concerning deep implantation of Gynemesh, a method that has not been validated by either controlled animal or human studies. Ethicon did not disclose to either surgeons or patients that it had not demonstrated the safety or efficacy of this novel method. Ethicon lacked evidence to support its claim that this novel incisional closure method reduced the potential of mesh exposure.

[125] ETH.MESH. 00658366

IFU Section: Three Levels of Vaginal Support and the GYNECARE PROSIMA Pelvic Floor Repair Learning Guide: Apical Support:

> ***There are 3 levels of support to the vagina commonly known for vaginal repair. Use of the GYNECARE PROSIMA System in a procedure is intended to provide level I and II of this support as follows": Level I support (upper third of vagina)."… "The GYENCARE PROSIMA SYSTEM uses the Mesh Implant straps to abut onto each obturator internus muscle and the overlying parietal fascia in the anterior vaginal repair, and Mesh implant straps abut the sacrospinous ligaments in the posterior vaginal repair. This provides direct support by suspension and indirect support by providing a broad area of Mesh Implant support for the upper vagina and uterus***

First and foremost it needs to be pointed out that Ethicon designed its studies to preclude the evaluation of level one support. The mean pre-operative POP-Q apical measurement, point C, in the Ethicon PROSIMA study (and extension study) was -3.9 cm.[126] This is considered stage one apical failure, a degree of level one support failure that is typically not associated with significant symptoms, a degree of level one support failure for which a patient would unlikely ever be offered surgery. It is also important to note that while the data collected in the Ethicon study with regard to level one support failed to demonstrate a significant improvement change in the POP-Q anatomic stage. The mean pre-operative and post-operative POP-Q for point C, the upper vagina or apex, remained unchanged. As noted earlier herein, the mean change in point C, from -4 to -6 has never been demonstrated to be of clinical significance. Of further importance is that this 2 cm change was only note in patients who underwent a combined anterior and posterior PROSIMA. Ethicon had and has no data to support the Claim that PROSIMA provides level one support. Ethicon only has limited and uncontrolled data to support the statement that, in patients with stage one apical failure who are typically asymptomatic and rarely if ever offered surgical

[126] Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.

intervention, a combined anterior and posterior PROSIMA device implantation may prevent progression to stage two apical prolapse at one year. The IFU claims that "the GYNECARE PROSIMA System in a procedure is intended to provide level I and II of this support" and "This provides direct support by suspension and indirect support by providing a broad area of Mesh Implant support for the upper vagina and uterus" are not supported by any clinical substantial clinical data and misleads the user of PROSIMA to believe that PROSIMA anterior or posterior may be used in a single compartment to treat apical prolapse. Ethicon did not disclose to either surgeons or patients that it had not demonstrated that the anterior or posterior PROSIMA could provide level one support.

Although internal Ethicon documents site their 1-year PROSIMA study to as evidence that PROSIMA provides apical support, the mean improvement in point C from -4 to -6 cm has never been shown to be of clinical significance and does not represent any change in POP-Q staging.[127] It is also important to note that this 2 cm improvement was only noted in patients who underwent combined anterior and posterior PROSIMA. The only finding with regard to the effect of PROSIMA at vaginal apex is that patients with stage one apical failure treated with combined anterior and posterior PROSIMA had not progressed to Stage 2 at the one-year follow-up appointment. Ethicon did not provide evidence support the claim that PROSIMA provides support to the upper vagina. Even if an argument was made that in the unique circumstance of combined anterior and posterior PROSIMA in patients with stage one apical failure (patients that would not be offered surgery for apical failure) PROSIMA stabilized the upper vault, the claims of PROSIMA's apical support would be misleading and, at most, a half-truth.

[127] ETH.MESH.08979440

By June of 2010, Ethicon was clearly aware that many physicians found the IFU misleading and that it was unable to support its misleading claims. On June 17th of 2010, Ethicon's Scott Prefer emailed Ethicon's PROSIMA product director, Kevin Frost, stating that he is "getting a lot of question as to whether or not PROSIMA is truly a level 1 support device." He states "I know the IFU states that it is indicated for both level 1 and 2 but the docs look at the mesh shape and tell me that it is not going to provide the support they are looking for especially at the apex. I have not been able to satisfy this objection." "It seems the word on the street is that PROSIMA is not enough support for the majority of defects that are being treated."[128] Rather than revising the IFU by removing misleading claims regarding level on support or initiating clinical trials to substantiate these claims, Kevin Frost sent out a mass internal email distributing a new professional education document that represented new misleading labeling, the GYNECARE PROSIMA Pelvic Floor Repair Learning Guide: Apical Support.[129]

GYNECARE PROSIMA Pelvic Floor Repair Learning Guide: Apical Support

In Ethicon's professional education document titled ***"GYNECARE PROSIMA Pelvic Floor Repair Learning Guide: Apical Support,"*** Ethicon represents that PROSIMA provides apical support. As discussed above, this is a misleading claim. This prof-ed document contains numerous misleading snapshots from the Ethicon PROSIMA study, snapshots provided to substantiate the PROSIMA claim to apical support.

[128] ETH.MESH.08961175
[129] ETH.MESH.08961175, ETH.MESH.08979440

"Point C: In the POP-Q system, the most distal edge of the cervix or vaginal cuff scar and is indicative of apical support" and "C remained well above the hymen (>3cm) in all patients."

Stating that, at one year following PROSIMA surgery, point C remained at least 3 cm above the hymenal ring suggests that PROSIMA is a good, and perhaps durable, treatment for the apex (providing level one support). However, what is conspicuously missing from this label (prof-ed document) is the fact that the mean measurement of point C prior to PROSIMA surgery was 3.9cm above the hymen, already approximately 1 cm above the hymen. The combined statements "Point C: In the POP-Q system, the most distal edge of the cervix or vaginal cuff scar and is indicative of apical support" and "C remained well above the hymen (>3cm) in all patients", misleads the end user to believe that PROSIMA treats apical vault failure. It is unlikely that any surgeon being called upon by a sales representative with this prof-ed document would be aware of the details of the Ethicon 1 year PROSIMA study. Therefore these surgeons would not know that point C was > 3cm from the hymenal prior to PROSIMA surgery and be effectively mislead by the claims.

"[A]ll mean POP-Q scores was significantly improved"

This statement provides that there was significant improvement in all points including the apex, point C. However, absent are the facts that there was no significant change between the pre-operative stage of the apex (mean stage one before and stage one after), the study appears to have excluded patients with anything more than stage one apical failure, and the authors concluded that they "could make no conclusion on the effects of PROSIMA on more advance stages of apical failure". In fact, the data suggests that the

study excluded patients with symptomatic apical failure and included no patients that would be considered for an apical support procedure. As discussed elsewhere herein, the only finding of Ethicon with regard to the effect of its PROSIMA on the vaginal apex is that patients with stage one apical failure treated with combined anterior and posterior PROSIMA had not progressed to Stage 2 at the one-year. The statement, "all mean POP-Q scores was significantly improved" effectively misleads the user to believe that PROSIMA is an effective option in treating apical vault failure.

IFU SECTION: Implant Placement:

"Plication of the pre-vesical tissue is not required".

Plication was performed in all of the observational studies of the inventor, Dr. Carey, prior to the Ethicon 1-Year study. The 1-Year Ethicon study permitted plication. Although that study does not report if plication was universally or episodically performed, there is no reason to believe that Dr. Carey changed his method for this study. Furthermore, if plication, for the first time, was not universally performed, it is reasonable to expect that Ethicon would have reported and analyzed the data of the two groups, plicated vs. not plicated.

The preponderance of the evidence suggests that plication continued to be performed on all patients. Regardless, the data prior to the 1-Year Ethicon study was based upon combined plication and PROSIMA and the 1-year study data was either based upon combined plication and PROSIMA or failed to report on its findings for those who did not undergo the combined procedure. As discussed earlier herein, the FDA has indicated that "Risk Message: should acknowledge uncertainties, including lack of currently available scientific knowledge". The IFU teaching of optional plication is not supported by the data and

represents inadequate directions for use, directions that may result in loss of efficacy, and is a statement of opinion.

"Preferably, the epithelium is closed in layers to obtain a relatively thick suture line at the site of the vaginal incision. Close the deeper layer using a continuous subepithelial non-interlocking stitch with suture such as 2-0 MONOCRYL suture or 2-0 MONOCRYL Plus Antibacterial (Poliglecaprone 25) Suture. Then close the epithelium by a non-interlocking continuous everting mattress stitch, using suture such as 2-0 coated VICRYL Suture or 2-0 Coated VICRYL Plus (Polyglactin 910) Antibacterial Suture".

Here Ethicon specifically teaches the surgeon away from the traditional closure methods used in vaginal surgery. Amongst the more common traditional closure methods is that of interrupted stitches, a method associated with a lesser degree of incisional ischemia (does not restrict important blood flow to the healing incision). Although there is a scientific rational that could be attached to an everting mattress closure therein taught by the PROSIMA IFU, elevation of the incision margins away from the mesh related inflammation, everting mattress closures are typically not performed as a continuous stitch. The teaching of the PROSIMA IFU not only directs the surgeon to perform a continuous mattress stitch but directs the surgeon to close the epithelium with two continuous layers of stitches. This novel double layered, continuous, epithelial closure method encourages a restriction of blood flow to the incision in excess of any traditional closure methods or methods taught in text books or manuals of pelvic surgery.

Although the use of subcutaneous stitches (typically interrupted and not continuous) had been commonly taught and utilized to reduce tension on an epithelial closure, this is quite distinct from placing a blood flow restricting stitch in the epithelium (beneath a subsequent epithelial stitch). Although it offers traditional closure as an alternative, it teaches its novel method as the preferred method. As discussed earlier herein, the FDA has indicated that

"Risk Message: should acknowledge uncertainties, including lack of currently available scientific knowledge". I can find no evidence that Ethicon studied its novel and concerning closure method. In its teaching of a double layered continuous stitch closure of the epithelium, Ethicon does not disclose to the surgeon that this is a novel method, and it has not validated this method by either observational cohort study or randomized controlled study.

IFU Section: Mesh Implant Hygiene

"During surgery, irrigate the vaginal wounds with saline. Keep the handling of the Mesh Implant to a minimum and practice good mesh hygiene."

Here Ethicon teaches vaginal wound irrigation with saline. This method was not included in any of the inventors published studies or in Ethicon's PROSIMA studies. I have trained over 1000 surgeons in pelvic reconstruction and have yet to encounter a surgeon that performed saline irrigation as part of his or her native tissue or mesh implantation vaginal surgeries. Ethicon therefore here teaches surgeons the addition of saline irrigation, a method that was not included in the publications of the prototype surgery or the PROSIMA surgery, a method with unknown effect on infection and wound healing in vaginal mesh implantation with or without a VSD. As discussed earlier herein, the FDA has indicated that "Risk Message: should acknowledge uncertainties, including lack of currently available scientific knowledge". I can find no evidence that Ethicon studied its novel method of saline wound irrigation in vaginal mesh implantation, a method that it had not used in its studies. Ethicon does not disclose that it has not validated this method by either observational cohort study or randomized controlled study. Additionally, instructions to "keep mesh handling to a minimum" is ambiguous and there is no definition of or standard in "good mesh hygiene."

IFU Section: VSD Fitting and Trimming.

"Proper size is achieved when the VSD fits snugly in the upper 2/3 of the distended vagina with the distal end and suture eyelets 1 cm above the hymenal ring (see Figure 13)". After the assembly is properly positioned in the upper 2/3 of the patient's distended vagina, secure the VSD in place by placing a single throw of suture through each VSD suture eyelet and into the posterior vaginal wall epithelium, laterally and above the hymen on each side, as shown in Figure 15".

The mean pre-operative total vaginal length of the Ethicon PROSIMA study was 8.2 cm. The PROSIMA IFU teaches that the VSD should be confined to the upper 2/3rd of the vagina. Using the study population as an example, the VSD would need to remain confined to the upper 5.5 cm of the vagina. The IFU also teaches that the suture eyelets located at the distal end of the VSD should located 1cm above the hymenal ring. This is a position that is located in the distal portion of the distal 1/3 of the vagina (SEE FIGURE 5). The IFU has is teaching a method that is impossible to execute. If the pessary is confined to the upper 2/3rd of the vagina, the distal end of the pessary can not be sutured to a point in the lower vagina 1 cm above the hymenal ring. Using the study population as an example, a VSD placed in the upper 2/3rd of the vagina would rest at least 1.5 cm above the suturing point taught by the IFU (SEE FIGURE 5).

As shown in the screen shots of from the 2009 IUGA Best Video presented by Ethicon's self-financed and managed Multicenter PROSIMA 1-Year trial, the instructed suturing of the VSD islets causes the vagina to be fixed in the distal 1/3 of the vagina, at the vaginal opening (FIGURE 6).[130] These instructions are confusing and teach a method that cannot be executed by the surgeon. If indeed Ethicon had validated the importance of

[130] https://www.youtube.com/watch?feature=player_embedded&v=MHiDdKHmUiQ, http://www.iuga.org/?page=video

maintaining the VSD in the upper 2/3 of the vagina, the second portion of its VSD placement instructions causes the surgeon to violate this important step and fix the pessary to the lower 1/3rd of the vagina.

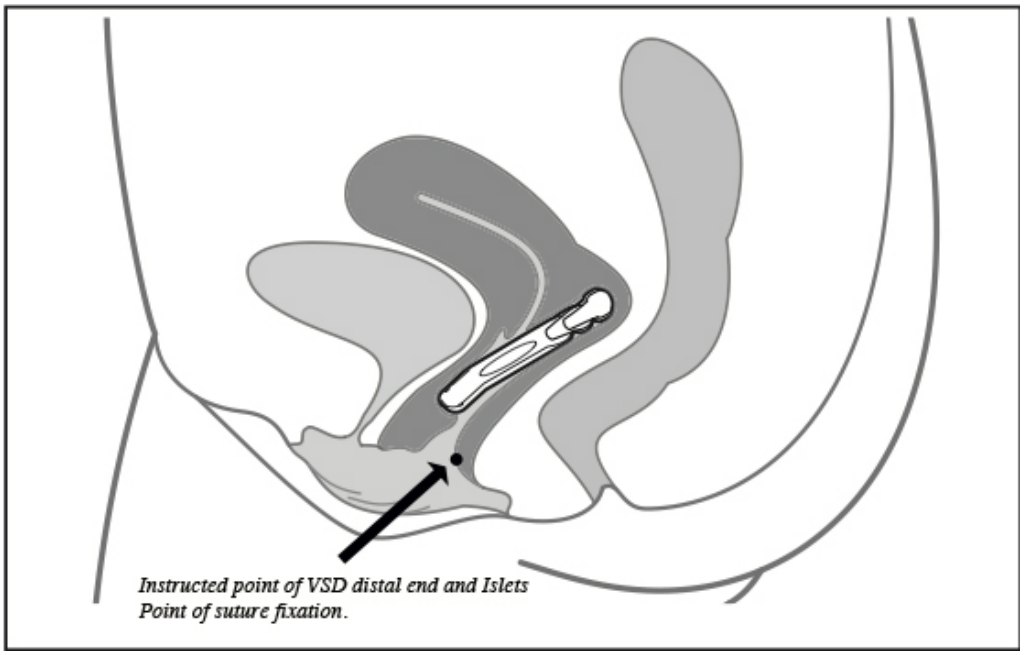

FIGURE 5

(PROSIMA IFU FIGURE 13*)

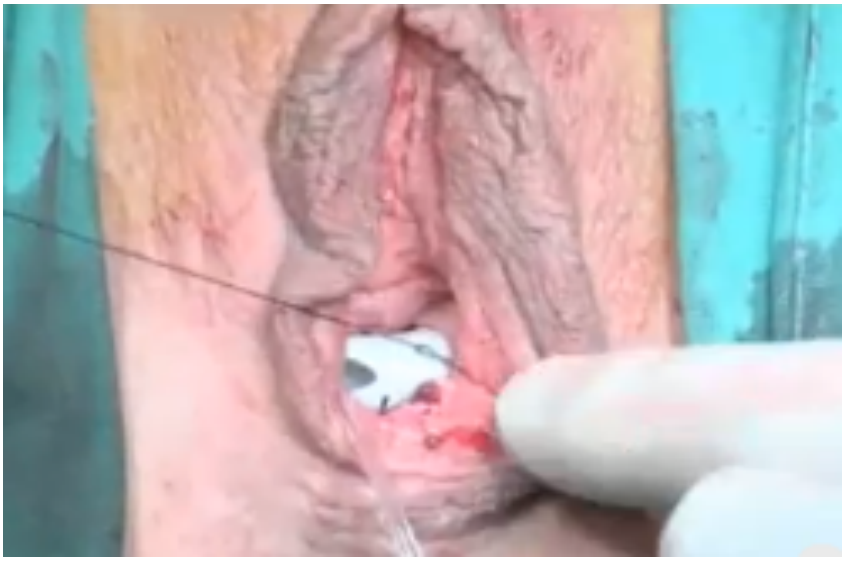

FIGURE 6

(PROSIMA SUB-INVESTIGATOR SECURES VSD AT TAUGHT BY IFU**)

IFU SECTION: PERFOMANCE

"Animal studies show that implantation of GYNECARE GYNEMESH PS elicits a minimal to slight inflammatory reaction, which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue. The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes".

This claim misrepresents the findings of Ethicon's rat study.[131] In this study performed by Ethicon it utilized a non-validated subjective grading system to measure inflammation. As discussed earlier, objective measurements such as inflammatory cells per high powered microscopic field were not reported. The Ethicon pathologist scored tissue reaction as 0 (normal or negligible), 1 (minimal), 2 (mild), 3 (moderate) or 4 (marked). Rats were euthanized at 7, 28, 63, and 91 days. Ethicon declared score differences of less than one not significant. Ethicon declared scores that were "not considered biologically significant." It is unclear why Ethicon would consider persistent but non-trending inflammation as insignificant.

In its IFU Ethicon claims that Gynemesh PS elicited a minimal to slight inflammatory reaction, which was transient. The Ethicon rat study did not find this. The Ethicon rat study did no have a grade defined as "slight". Scoring by the Ethicon pathologist included minimal to mild inflammation that persisted through the entire study period of 91 days. The inflammation was not transient. Furthermore, this inflammation at 91 days would not be expected in normal wound healing. Ethicon describes in its IFU

[131] Barbolt, T A., Biology of polypropylene/polyglactin 910 grafts. Int Urogynecol J (2006) 17: S26–S30

claim a "deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh." Yet, in its rat study involving the implantation of several different types of mesh, Gynemesh PS was the only mesh associated with an actual reduction of connective tissue. In response to this concerning finding, Ethicon offered this in its 510(k) application: "the presence of minimal fibrous connective, in close association with the elements of the mesh, is considered to be adequate for integration of the mesh with surrounding tissues."[132] Recent studies have validated this unique trait of Gynemesh PS, its ability to result in the loss of fibrous tissue.[133] Ethicon claims that wound healing is not noticeably impaired, yet incisional separation with associated mesh extrusion is reported to occur in up to 25% of cases of Gynemesh PS implantation while incisional separation is almost unheard of in native tissue prolapse surgery.[134] Furthermore, Ethicon introduced with PROCIMA a novel wound closure technique designed in attempt to deal with the known issue of mesh related wound healing. Ethicon claims that the mesh remains soft and pliable. As discussed elsewhere in this document, polypropylene mesh the medical and scientific literature has demonstrated that polypropylene does not remain soft and pliable and this is consistent my findings with the hundreds of pieces of mesh, including Gynemesh, I have explanted. The claim that the Gynemesh PS does not degrade is in contradiction to many scientific reports of implanted polypropylene mesh, is inconsistent with Ethicon's own internal studies and

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[132] ETH. M ESH.05512282

[133] Liang, Rui, Wenjun Zong, Stacy Palcsey, Steven Abramowitch, and Pamela A. Moalli. "Impact of Prolapse Meshes on the Metabolism of Vaginal Extracellular Matrix in Rhesus Macaque." Obstetrical & Gynecological Survey 70.6 (2015): 385-87.
**https://www.youtube.com/watch?feature=player_embedded&v=MHiDdKHmUiQ,
http://www.iuga.org/?page=video

[134] The Prolift Surgeons Monograph ETH.MESH.00658363, an Ethicon publication, discloses a 3-17% incidence of mesh erosion. C.R. Bard found poor wound healing associated with vaginal mesh to be worth of its own name, "Persistent Delayed Healing" coined PDH.

documents and contrary to the testimony of Ethicon's former scientist, Thomas Barbolt, who testified under oath

> **Q. And that's Ethicon's position as you – as the spokesperson for Ethicon, it's Ethicon's position that degradation, surface degradation, can occur, correct?**
>
> **A. Yes.**[135]

The multiple claims of the PROSIMA IFU PERFORMANCE section are misleading and provide a false impression in the mind of the reader. Furthermore, Ethicon does not disclose in its IFU the facts of its animal study that convey an opposing message.

IFU SECTION: Balloon Inflation

"Once deployment is confirmed, remove finger and continue to inflate the Balloon fully until only a fingertip fits snugly at the introitus between the Balloon and the vaginal wall. Stabilization of the VSD is recommended as inflation occurs. The inflated Balloon serves to abut the Mesh Implant onto the vaginal wall. The volume of air required to sufficiently inflate the Balloon will vary from patient to patient". "NOTE: The maximum Balloon inflation volume must not exceed 90". "At any time the Balloon may be palpated or visually inspected to ensure it has maintained sufficient inflation. NOTE: As the patient moves, the Balloon will settle in the vaginal cavity and may appear to either increase or decrease in pressure. This is normal".

This instruction provides neither a safe nor reproducible method of balloon inflation. This instruction teaches that the "inflated balloon serves to abut the Mesh Implant onto the vaginal wall" and "to inflate the Balloon fully until only a fingertip fits snugly at the introitus between the Balloon and the vaginal wall". Here Ethicon teaches that the surgeon should measure pressure at the vaginal opening with his or her finger. Firstly, the pressure at the vaginal opening has never been demonstrated to be the same as or proportional to any specific pressure on the vaginal wall. Secondly, "snugly" is an ambiguous that provides

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[135] Deposition of Thomas Barbolt, Ph.D., January 8, 2014, at 409:2-8

no means of reproducibility between users. Ethicon failed to provide a validated and reproducible method for balloon inflation. By way of example, a simple pressure valve, an off-the-shelf item, affixed to the filling syringe would provide an objective and reproducible method for filling the balloon to known pressure, a pressure that Ethicon should have validated in a randomized controlled trial. Ethicon, at a minimum, recognizes that excess pressure is dangerous (as discussed in Warnings and Precautions) and provides, "NOTE: The maximum Balloon inflation volume must not exceed 90 ml". Yet even in its admonition of risks associated with high balloon pressures, Ethicon fails to provide a safe and reproducible method for protecting against a known critical pressure. Vaginal size is not the same between any two patients and, therefore, while 90ml cause a safe pressure in one patient, it may provide an unsafe pressure in another. I can find no evidence in the Ethicon 1-Year and follow-up study or in the studies of Dr. Carey that proceeded such, that a maximum volume of 90ml was validated as a volume that provided safety and effectiveness across a broad range of vaginal sizes. It is certainly possible that complications and efficacy were related to balloon inflation volumes (pressures). However, this data was not collected. Ethicon herein has provided ambiguous an inadequate directions.

IFU SECTION: WARINGINGS AND PRECAUTIONS:

"The Balloon inflation maximum is 90 mL. Do not over-inflate the Balloon. Excessive inflation of the Balloon may cause patient discomfort, tissue necrosis, disruption of vaginal wound postoperatively, or inability to void".

Here Ethicon discloses a concern of serious complications associated with high balloon pressures. However, Ethicon provides no reasonable or reproducible means to protect against high balloon pressures. "90mL" will not a pressure and pressure at 90ml

will be very different from one patient to the next (vaginal sizes vary). Although Ethicon may provide that this arbitrary maximum with its resultant unknown range of pressures was used safely and effectively in its 1-Year study, this would not be a valid statement. Mesh exposure was noted in 8% of patients. As Ethicon did not test different balloon volumes and pressures, it is reasonable that a volume of less than 90mL was associated with disruption of wounds and mesh exposure. Likewise, Ethicon cannot state that discomfort, de-novo dyspareunia, or surgical failure was not associated with a balloon volume of less than 90mL. Although a simple, off-the-shelf pressure valve attached to the filling syringe may have been used to validate safety and efficacy of balloons filled to a known pressure and provided a reproducible means of balloon filling, this method was not part of the PROSIMA study.

Although Ethicon could have tested safety and efficacy over a range of maximum and minimum balloon volumes, such was not part of the PROSIMA study. Although Ethicon is clearly concerned and teaches that significant complication can occur with high balloon pressure, it does not teach a reproducible method of maintaining a pressure below a critical value that it had demonstrated to be safe and effective. The directions do not provide a method by which the user can safely and effectively use the balloon, tends to cause the user to have the false impression that inflation below 90mL will provide safety across differing vaginal sizes, and do not disclose that the maximum balloon volume had not been evaluated and therefore remains uncertain. This section of the IFU is therefore both inadequate and misleading.

"Do not use the GYNECARE PROSIMA System if you think the surgical site may be infected or contaminated. If the Mesh Implant or VSD-Balloon Assembly is used in contaminated areas it must only be with the understanding that subsequent infection may require its removal. Acceptable surgical practice should be followed for the

GYNECARE PROSIMA System as well as for the management of infected or contaminated wounds."

The event of transvaginal mesh implantation marked a new and dangerous moment in mesh implantation surgery. The standard of prosthetic implantation surgery had been to never implant through a contaminated wound. The risks of severe infection outweighed any benefits. All vaginal wounds are considered clean-contaminated. Transvaginal mesh implantation was a deviation from the traditional abdominal mesh implantation surgeries that implanted through clean rather than clean-contaminated wounds. The instructions in this warning section state that if the PROSIMA "is used in contaminated areas it must only be with the understanding that subsequent infection may require its removal". This statement is problematic. This statement suggests that the normal situation is implantation through a clean non-contaminated wound and that the surgeon should beware of a specific and possible situation. This statement also provides that removal may be required but neither provides instructions for removal nor discloses that very few surgeons will be capable of removing an implant in its entirety.

Unlike the vast if not all of surgeries trained in surgical residency programs, this surgery involved the implantation of a foreign body prone to fibrosis and contraction into blind spaces. Although many subspecialists have unique training and experience in dissecting and visualizing the full extent of the arcus tendineus fascia pelvis and sacrospinous ligament coccygeus muscle complex, a dissection and visualization that is requisite to any attempt at complete PROSIMA removal, very few general gynecologist and urologists have this experience and skill set. Yet this is the exact group of surgeons that Ethicon targeted in its sale of PROSIMA. On February 10th of 2009, Andrew Meeks (U.S.

Director of Professional Education) wrote to Jonathan Meeks (Ethicon World Wide Marketing Director) "The target audience appears to be less skilled generalists. At a time when the scrutiny against mesh is at an all time, high, why would we want to put a product with questionable data in this groups hands?"[136] This messaging can be traced back to the time of product inception. On September 6th of 2005, Kim Hunsiker (Ethicon Director of Clinical Programs) emailed her colleagues, "Discussed with the inventors and marketing. The main targets will be those doing non mesh anterior and posterior repairs".[137] This is a group of surgeons who are not operating in the areas of the sacrospinous ligament or arcus tendineus fascia pelvis and is predominantly represented by non sub-specialist gynecologists and urologists. Furthermore, this clearly represents a group of surgeons without mesh experience, who would be unaware of the difficulties of mesh removal surgery.

Although Ethicon did not provide instructions for removal of PROSIMA nor warn of said difficulties, it did understand that its target audience was not trained in the anatomic landscape of PROSIMA. In its internal PowerPoint presentation (pre launch of PROSIMA), Project New MINT GAT Update, it displayed "Moving target audience from suture world to mesh world ; increase knowledge required on diagnosis, dissection and placement of mesh".[138] The instructions of this warnings section create a false impression that the normal use of the product would not be in a clean-contaminated field and not incur the risks therein warned. The instructions of this warning create the false impression that the PROSIMA will be removable, or, at least, do not provide the material fact associated with removal. The target audience of Ethicon is the less skilled general gynecologist and

[136] ETH.MESH.00548923
[137] ETH.MESH.03048784
[138] ETH MESH 03048943

urologist without experience in implanting or explanting mesh. This is a group uniquely susceptible to misleading information and the development of a false impression. The directions do not provide a instructions by which a user may safely and effectively remove PROSIMA. Although Ethicon knew it was marketing to a unique group of surgeons particularly vulnerable to false impressions, at risk of being mislead, and knew they would require additional knowledge, it did not provide such.

"Although bladder injury is unlikely to occur with this technique, cystoscopy is recommended to be performed."

As noted elsewhere herein, Ethicon's specifically targeted less skilled gynecologists, surgeons who were performing only native tissue anterior and posterior repairs. This is a group of surgeons that, with rare exception, have neither substantial train in nor privileges to perform cystoscopy. Ethicon is hence targeting a group of surgeons that will be unable to perform a portion of the procedure recommended in its warnings and precautions.

"Prophylactic antibiotics can be administered according to the surgeon's usual practice."

All published studies including the prototype studies of Dr. Carey and the Ethicon 1-Year PROSIMA study used a prophylactic antibiotic regimen. The patients in the prototype Dr. Carey studies all received intravenous pre-operative antibiotics, an additional 48 hours of post-operative intravenous antibiotics, and another 5 days of oral antibiotics. Although antibiotics were mandatory in the Ethicon 1-Year PROSIMA study, the regimen is not reported. Hence, any and all claims of efficacy and safety of the PROSIMA device and method are attached to the use of prophylactic antibiotics. The IFU instruction that

"antibiotics can be administered according to the surgeon's usual practice" does not disclose that all claims of efficacy and safety of the PROSIMA device and method are attached to the use of prophylactic antibiotics, and therefore said instructions do not provide a means by which the surgeon can safely and effectively implant PROSIMA; Ethicon does not disclose that the claimed benefits of PROSIMA without the use of antibiotics remains uncertain. The instruction encourage the surgeon perform his usual method rather than the tested method of PROSIMA.

IFU SECTION: ADVERSE REACTIONS

"Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pain with intercourse and pelvic pain. These may be self-resolving over time."

Ethicon here misleads the user to the false impression that the adverse reactions associated with PROSIMA are the same as those typically associated with prolapse repair procedures. As discussed elsewhere herein, one of Ethicon's key target users for PROSIMA was the less skilled surgeon doing native tissue (no mesh) prolapse repair surgery. Many adverse reactions of PROSIMA are not typical of native tissue prolapse surgery. Infection is frequently seen with mesh implantation surgery (e.g. PROSIMA). Infection is sufficiently rare in native tissue surgery that many surgeons will expend their entire career without seeing an infection. In addition, infections that occur with PROSIMA are not those that occur with native tissue prolapse surgery. Whereas mesh related infections rarely resolve without surgical intervention, the rare native tissue infection almost never requires surgery. Incisional dehiscence is so common in mesh related surgeries that one manufacturer, C.R. Bard, developed a phraseology and narrative to describe it, Persistent Delayed Healing, and another manufacturer, Ethicon, taught a

novel double layered epithelial closure in attempt to prevent it. Incisional dehiscence is rare in native tissue prolapse surgery. In addition, whereas mesh related incisional dehiscence requires surgical intervention in the majority of cases, native tissue incisional separation rarely requires surgery.

Ethicon specifically calls out pain with intercourse and pelvic pain as two adverse reactions of PROSIMA that are those typically associated with other prolapse surgeries. Many investigators, including the one of the inventors of Ethicon's Prolift, Jaquetin,[139] have demonstrated that mesh related dyspareunia occurs more commonly than that of native tissue surgery. However, even if the incidence of mesh related dyspareunia and pelvic pain had been shown to be no different than that of native tissue surgery, it is incorrect to state that this dyspareunia and pelvic pain is that typical of native tissue prolapse surgery. Pain with intercourse and pelvic pain caused by polypropylene mesh is very different than that associated with native tissue surgery. Mesh is plastic and, shortly after implantation, creates severe scarring, contraction, and loses elasticity. Vaginal contraction and pain associated with vaginal mesh implantation responds poorly to conservative therapy and often, up to 50% of the time, does not respond to surgical intervention.[140] Pain following native tissue surgery is most commonly not secondary to severe scarring or contraction but rather from overzealous trimming of vaginal mucosa or plication of the levator ani muscles. This pain responds well to conservative therapy and surgery is rarely necessary. In summary, the incidences, consequences, and treatments of

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[139] Fatton B, Lagrange E, Jacquetin B. Sexual Outcome After Transvaginal Repair Of Pelvic Organ Prolapse (Pop) With And Without Mesh: A Prospective Study Of 323 Patients. Department of Gynecology. University Hospital of Clermont-Ferrand. France. Department of Gynecology. University Hospital of Clermont-Ferrand. France. http://www.ics.org/Abstracts/Publish/105/000053.pdf

[140] Crosby, Erin C., Melinda Abernethy, Mitchell B. Berger, John O. Delancey, Dee E. Fenner, and Daniel M. Morgan. "Symptom Resolution After Operative Management of Complications From Transvaginal Mesh." Obstetrics & Gynecology 123.1 (2014): 134-39.

common adverse reactions of transvaginal polypropylene mesh implantation are unique and not those typical of general pelvic organ prolapse surgeries, or more specifically, the pelvic organ surgeries of the targeted PROSIMA user, native tissue colporrhaphies. The GyneMesh of the PROSIMA device is associated with all known complications of transvaginal polypropylene mesh implantation. In addition to the above noted information demonstrating the misleading information disseminated by the claims of Ethicon, it is also important to note that Ethicon did not perform a single observational controlled study or randomized controlled trial to demonstrate that its novel PROSIMA procedure with its Gynemesh PS was associated with adverse reactions typical of pelvic organ prolapse surgery with or without mesh.

"Potential adverse reactions are those typically associated with surgically implantable materials, including infection potentiation, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that result in implant contraction."

This statement is both ambiguous and misleading. It does not specify what type of surgical implantable materials are the comparators. The statement is misleading and gives the false impression that PROSIMA Device with Gynemesh PS implant is associated with the same adverse reactions as other implantable materials. This is not true and especially concerning as Ethicon is targeting the implanters of biologic grafts.[141] Biological implants have very different adverse reactions than polypropylene mesh (PROSIMA). By way of example, mesh related incisional dehiscence and or extrusion may occur in up to

[141] 112240 Intro to Prosima Nov 2005. In this 2005 internal Ethicon PowerPoint presentation, GYNCARE PROSIMA, it is shown that one of the main targets of PROSIMA sales is "current non-synthetic graft users". ETH.MESH.03048784: Ethicon's Director of Clinical Programs, Kim Hunsiker, emailed her collegues, "Discussed with the inventors and marketing. The main targets will be those doing non mesh anterior and posterior repairs". Many of non-mesh surgeons were biologic users.

25% of transvaginal mesh implant surgeries and rarely heal spontaneously.[142] Most studies, including the PROSIMA study, demonstrate a 50-75% incidence of subsequent procedural or surgical intervention.[143] Biological graft incisional dehiscence and or extrusion is uncommon and typically heals spontaneously rarely requiring procedural or surgical intervention.[144] Hence, the complication of incisional dehiscence and extrusion not only occurs with much greater incidence with polypropylene mesh, but represent a different type of complication. These very different adverse reactions and consequences are described consistently in the medical literature and are consistent with my extensive clinical experience implanting both biologic and polypropylene grafts. Likewise, the incidence and type of inflammation that occurs with mesh is quite distinct from that of biologic grafts. Whereas chronic inflammation has not been demonstrated with biologic grafts, polypropylene mesh implantation is always associated with chronic inflammation. Whereas biologic graft material has never been associated with severe contraction,

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[142] Miller D., et al. Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse - 5-Year Results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143., Svabik K. Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014; 1-7. DOI: 10.1002/uog.13305. Simone Dos Reis Brandão Da Silveira, Jorge Milhem Haddad, Zsuzsanna Ilona Katalin De Jármy-Di Bella, Fernanda Nastri, Miriam Goncalves Markos Kawabata, Silvia Da Silva Carramão, Claudinei Alves Rodrigues, Edmund Chada Baracat, and Antonio Pedro Flores Auge. "Multicenter, Randomized Trial Comparing Native Vaginal Tissue Repair and Synthetic Mesh Repair for Genital Prolapse Surgical Treatment." International Urogynecology Journal Int Urogynecol J 26.3 (2014): 335-42.

[143] Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8., Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." International Urogynecology Journal Int Urogynecol J 24.10 (2013): 1679-686.

[144] Gomelsky A, Rudy DC, Dmochowski RR. Porcine dermis interposition graft for repair of high grade anterior compartment defects with or without concomitant pelvic organ prolapse procedures. J Urol. 2004;171:1581-1584.

Gandhi S, et al. A prospective randomized trial of solvent dehydrated fascia lata for the prevention of recurrent anterior vaginal wall prolapse. Am J Obstet Gynecol. 2005;192:1649-1654. Clemons JL, Myers DL, Aguilar VC, Arya LA. Vaginal paravaginal repair with an AlloDerm graft. Am J Obstet Gynecol. 2003;189:1612-1618.

transvaginal polypropylene mesh is implantation has been associated with 30-50%, and up to 85% contraction.[145] The claims of this warning are ambiguous, create a false impression amongst a targeted group of physicians particularly susceptible to misleading information, and do not reveal the material facts.

IFU Missing Information

Prior to any substantial sales of PROSIMA there was published evidence that smoking was associated with a significant increase in the risk of mesh extrusion.[146] This was later validated in a study performed by a paid consultant of Ethicon in a prospective study using the Gynemesh PS material.[147] Although smoking is not the cause of mesh extrusion, it is associated with a significantly increased risk of mesh extrusion. Ethicon did not include this important warning in its IFU.

VSD VS PESSARY LABELING

The VSD is most similar to a vaginal pessary. As discussed elsewhere in this monograph, the PROSIMA VSD shares very little in common with the Silimed Vaginal Stent. Although the form and function of many tradition pessaries are almost identical to that of the VSD, pessaries do not have post-surgical indications. Hence, Ethicon could not claim a pessary as a predicate device. Nonetheless, as the VSD is almost identical to many

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[145] Klinge U, Klosterhalfen B, Muller M, Ottinger AP, Schumpelick V (1998) Shrinkage of polypropylene mesh in vivo: an experi- mental study in dogs. Eur J Surg 164:965–9. Letouzey V, Deffieux X, Levailolant J, et al. Overview of transvaginal placement of reconstructive materials (surgical mesh or biografts) for treatment of pelvic organ prolapse or stress urinary incontinence. nt Urogynecol J Pelvic Floor Dysfunct. 2009;20:S205.

[146] Araco, Francesco, Gianpiero Gravante, Roberto Sorge, John Overton, Davide De Vita, Mario Primicerio, Stefano Dati, Placido Araco, and Emilio Piccione. "The Influence of BMI, Smoking, and Age on Vaginal Erosions After Synthetic Mesh Repair of Pelvic Organ Prolapses. A Multicenter Study." Obstetrical & Gynecological Survey 64.11 (2009): 721-22.

[147] Marie¨lla I. Withagen, MD, Mark E. Vierhout, MD, PhD, Jan C. Hendriks, PhD, Kirsten B. Kluivers, MD, PhD, and Alfredo L. Milani, MD. Risk Factors for Exposure, Pain, and Dyspareunia After Tension-Free Vaginal Mesh Procedure. Obstet Gynecol 2011;118:629–36.

pessaries in both form in function and the VSD has shares almost no form with the Silimed vaginal stent, Ethicon should have included in its labels much of the important information provided in the pessary labels. Alternatively Ethicon could have conducted studies to demonstrate that the post surgical use of its VSD (pessary) did not require such information. Ethicon did neither.

The Silimed Vaginal Stent is a Silicon Elastomer balloon.

The VSD and the Cooper Surgical Milex Pessaries (below) are both Semi-rigid Silicon Vaginal support devices (FIGURE 7)

The Silimed Vaginal Stent[148] (proposed VSD predicate device)

[148] From the Silimed website: http://www.silimed.com.br/en/urology/
*** The accessory, balloon, has been digitally removed to show the unobscured VSD
^ Cooper Miles pessaries, Cooper Surgical, Regula and Ring With Support

The Ethicon VSD***

Cooper Regula Pessary^

Cooper Ring Pessary^

FIGURE 7

PESSARY COMPARISON

Pessary[149] vs. VSD Patient Labeling:

CONTRAINDICATIONS:

Pessary: *"The presence of infections or lacerations"*

VSD: *"The GYNECARE PROSIMA System should not be used in the presence of pregnancy or purulent infections or cancers of the vagina, cervix, or uterus".*

[149] Cooper Surgical. Fitting Instructions for the Health Care Professional. 37801 • Rev. A • 9/12 and 37800 • Rév. A • 9/12

The cooper pessaries labeling of its devices representative of pessaries legally marketed in the U.S. for decades, the medical devices nearly identical to the VSD in form, fit, and function, taught that use was contraindicated with a laceration. Ethicon not only excludes this teaching from its patient labeling, but taught use of its VSD device directly on top of a laceration. Merriam Webster dictionary offers "incision" as its first synonym for laceration.[150] I can find no evidence that Ethicon performed testing or conducted any studies to demonstrate that this historical contraindication did not apply to its pessary, the VSD. As noted elsewhere in this monograph, the FDA indicates that contraindications must be included in the IFU and, that if there are differences of opinion regarding the use on of a pessary (VSD) on top of a laceration (incision) , it must report the existence of difference in opinions. The failure to provide such information, relevant material facts and uncertainties is considered misbranding.

Whereas Cooper taught that infection was a contraindication, Ethicon taught only purulent infection. The teaching of Ethicon is in contradiction to the historical teachings and contraindications of pessary devices. Ethicon here teaches that the its VSD (pessary) may be used concurrent to a vaginal infection that is not productive of puss. I can find no evidence that Ethicon performed testing or conducted any studies to demonstrate that this historical contraindication did not apply to its pessary, the VSD. As noted elsewhere in this monograph, the FDA indicates that contraindications must be included in the IFU and, that if there are differences of

[150] "Synonym for Laceration." Merriam Webster, n.d. Web. < http://www.merriam-webster.com/dictionary/laceration;.

opinion regarding the use on of a pessary (VSD) with an ongoing non-purulent infection, it must report the existence of difference in opinions. The failure to provide such information, relevant material facts and uncertainties is considered misbranding.

FITTING:

Pessary: "*The patient should be informed that it is not uncommon to have to change the size or type of pessary more than once after being originally fitted. This is why it is so important that your patient be instructed to return within 24 hours of the initial fitting and again in 72 hours". "The health care professional should be able to sweep one finger between the pessary and vaginal walls. It there is not enough space to do this, the next smaller pessary should be tried".* Most pessaries are available in 7-13 sizes. The Regula pessary was available in 5 8sizes and the Ring pessary was available in 13 sizes.

VSD: Ethicon does not teach any repeat examination or repeat fitting of its VSD. Whereas historical teaching, as reflected in the Cooper IFU, guards against pressure and ulceration, "*The health care professional should be able to sweep one finger between the pessary and vaginal walls",* Ethicon teaches *"Proper size is achieved when the VSD fits snugly in the upper 2/3 of the distended vagina".* In recognition of the great variation of vaginal size and shape, Cooper Surgical has marketed over 12 different pessary shapes available in 7-13 different sizes. Ethicon's VSD could

be disposed in only 3 sizes. I can find no evidence that Ethicon performed testing or conducted any studies to demonstrate that the historical teachings of pessary fitting did not apply to its VSD, and its VSD could be safely and effectively used with its novel abbreviated sizing and abandonment of the traditional repeat examination (and refitting). The FDA indicates that that if there are differences of opinion regarding the fitting of the VSD (pessary), it must report the existence of difference in opinions and also reveal the material facts. The failure to disclose the existence of differing opinions, the material facts, and the uncertainties represents misbranding. With an incidence of pessary related ulceration occurring as often as 9%, the abandonment of traditional fitting and follow-up is of concern.

PATIENT INSTRUCTIONS:

Pessary: "*Have the patient report any of the following, any difficulty urinating, any changes in color or consistency of vaginal discharge, any increase in amount of vaginal discharge, any foul odor associated with vaginal discharge, vaginal itching".*

VSD: *"The VSD may cause a discharge from the vagina. This discharge will disappear after the VSD is removed", "if the VSD is causing significant discomfort or concern you should contact your doctor", "It is advised to avoid sexual intercourse for at least six weeks following surgery".* It is unclear why Ethicon

dismissed the traditional patient instructions on difficulty with urination. It is unclear why Ethicon dismissed the traditional patient instructions to report the signs and symptoms of infections and ulceration including changes in color, consistency, and or amount of vaginal discharge. I can find no evidence that Ethicon conducted and testing or studies to demonstrate that the historical concerns with pessaries regarding the signs and symptoms of infection did not apply to its pessary, VSD, novelly disposed on top of a surgical incision and a foreign body implanted through a clean-contaminated wound. Ethicon did not disclose the material facts regarding its decision to disregard traditional patient teaching and created the false impression that a patient need not be concerned about several important warning signs of infection and ulceration. The failure to disclose the material facts and the creation of false impression represents misbranding.

OBJ OBJ

EXPERT OPINIONS AND CONCLUSIONS

EXPERT OPINION 1 : THE LABELING WAS DEFECTIVE:

As described in this monograph, the PROSIMA labeling was misleading and defective. The IFU:

- Did not provide the necessary information required for the surgeon and patient to use the device safely and for the purposes for which it is intended
- Did not disclose relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended.
- Claimed unsubstantiated therapeutic benefit
- Did not disclose significant warnings and complications
- Used ambiguous language
- Failure to inform the consumer of the facts that are relevant to those statements actually made
- Create a false impression in the mind of the reader
- Failure to reveal material facts
- Failed to reveal consequences that may result from use
- Failed to reveal the existence of a difference of opinion
- Made false representations

Based on my knowledge, training, experience, review of the medical, scientific and regulatory literature, and review of internal documents I state with reasonable degree of medical certainty that the PROSIMA device labeling was misleading and defective.

EXPERT OPINION 2 : ETHICON KNOWINGLY PROVIDED INCORRECT, INSUFFICIENT AND DECEIVING INFORMATION TO THE FDA IN ORDER TO RAPID GAIN CLEARANCE FOR MARKETING AND BYPASS THE PMA PROCESS.

As described in this monograph, Ethicon knowingly provided false information to the FDA to gain a SE determination.

- PROSIMA was not SE the combination of GyneMesh PS device and Silimed Vaginal Stent.
- The PROSIMA VSD did not have the same technical characteristics of the Silimed Vaginal Stent
- The PROSIMA VSD did not have the same indications as the Silimed Vaginal Stent

Based on my knowledge, training, experience, review of the medical, scientific and regulatory literature, and review of internal documents I state with a reasonable degree of medical and industry certainty that Ethicon knowingly provided incorrect, insufficient and deceiving information to the FDA in order to gain rapid clearance for marketing and bypass the PMA process. Furthermore, based on my knowledge, training, experience, review of the medical, scientific and regulatory literature, and review of internal documents, I state with a reasonable degree of medical and industry certainty, that Ethicon marketed the PROSIMA device without first demonstrating that

such device was safe and effective and that such demonstration of safety and efficacy is an industry standard that is separate and distinct from federal guidance and law.

EXPERT OPINION 3: THERE WAS NOT SUFFICIENT DATA TO SUPPORT THE USE OF THE PROSIMA DEVICE IN HUMANS.

As described in this monograph, the biased clinical data failed to provide reasonable evidence that PROSIMA was as safe and effective as other surgical methods.

- There is no level one evidence in support of the PROSIMA device and method.
- All evidence is in the form of uncontrolled observational data from financially incentivized investigators and authors or the manufacturer itself.
- The only published study on the cleared PROSIMA device and method failed to reach its predetermined success end point.
- The only published study on the cleared PROSIMA device and method failed to demonstrate long term efficacy that was equal to or greater than existing devices and methods
- Level one data existed to demonstrate that other devices and methods were more efficacious than PROSIMA.
- The FDA notified Ethicon of the need for level one data in support of the safety and efficacy of PROSIMA.

- Ethicon was unable to demonstrate the existence of such data.
- Ethicon opted not to initiate the necessary trials to to demonstrate the safety and efficacy of PROSIMA

Based on my knowledge, training, experience, review of the medical, scientific and regulatory literature, and review of internal documents I state with a reasonable degree of medical that there was not sufficient data to support the use of the PROSIMA device in humansAs the PROSIMA device meets the definition of a significant risk device, is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, it is also my opinion to a reasonable degree of medical certainty, that Ethicon knowing falsely represented its PROSIMA as a NSE device and bypassed the need for applying for an IDE with the FDA. This application would certainly have been a red flag to the FDA with regard to the PROSIMA claims of substantial equivalence.

EXPERT OPINION 4: THE VSD and VSD METHOD WERE DEFECTIVE

As described in this monograph, the VSD did not share form, fit, or function with its proposed predicate. Whereas the proposed predicate was a fluid filled balloon splint that providing 12 weeks of pressure on the vaginal walls, the VSD was not a balloon but rather a semi-rigid pessary (by form, shape, and function). Ethicon taught that its PROSIMA Gynemesh PS was to be places in the proximal 2/3rd of the vagina but taught that its PROSIMA VSD should be secured to the distal 2/3rd of the vagina. Hence, the

PROSIMA VSD was not capable, in its form or placement, of providing the intended support, support that could have been provided by its proposed predicate device.

Based on my knowledge, training, experience, review of the medical, and scientific, and review of internal documents I state with a reasonable degree of medical that the PROSIMA VSD and VSD Method were defective.

EXPERT OPINON 5: THE PROSIMA DEVICE AND METHOD WERE DEFECTIVE

As described in this monograph, the PROSIMA device and method combined a defective synthetic transvaginal implant, and implant prone to bodily injury including severe inflammation, infection, erosion, scarring and pain with an experimental vaginal splint that was similar in form, fit (although defectively fit), and function to a pessary, a medical device associated with bodily insult including, inflammation, infection, and ulceration. This novel and experimental device and method added insult to injury. Ethicon never performed a controlled observational study or randomized controlled trial to evaluate the safety and efficacy of this dangerous combination.

In addition, the overwhelming pool of level one data fails to demonstrate any subjective benefit of transvaginal mesh surgery over native tissue surgery. Yet, there is ample level one evidence to demonstrate a significantly higher rate of complications including de novo dyspareunia, mesh erosion, vaginal contraction, de novo urinary incontinence, increased blood loss, and increased operative time.

Transvaginal polypropylene mesh implantation in the treatment of pelvic organ prolapse is uniquely associated with a dramatically increased risk of de-novo pelvic organ prolapse in the untreated compartment. This incidence may be as high as 40%.[151] Of great concern it that Dr. Carey, the inventor of the PROSIMA method, reported a 33% incidence of untreated posterior compartment failure in his 2007 study, yet Ethicon chose not to report untreated compartment failure in its PROSIMA 1-Year observational study, its only study on PROSIMA.[152]

Based on my knowledge, training, experience, review of the medical, and scientific literature, and review of internal documents I state with a reasonable degree of medical that the PROSIMA device and method were defective.

EXPERT OPINION 6: THE PROSIMA GYNEMESH PS MATERIAL WAS DEFFECTIVE

The Fiber Was Defective.

When choosing a material for permanent implantation in the human body, one must take into consideration how that material will effect the body, how the body will effect that

[151] Withagen, M, et al. Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse. Amer Coll Obstet and Gyn 2011; 117:No2,Pt1;, Vollebregt, A., K. Fischer, D. Gietelink, and Ch Van Der Vaart. "Primary Surgical Repair of Anterior Vaginal Prolapse: A Randomised Trial Comparing Anatomical and Functional Outcome between Anterior Colporrhaphy and Trocar-guided Transobturator Anterior Mesh." BJOG: An International Journal of Obstetrics & Gynaecology 118.12 (2011): 1518-527.

[152] Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397. Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.

material, and how that material's properties compares to the properties of the native tissue it is replacing.

Polypropylene Has an Adverse Effect on the Human Body. As described earlier in this report, the innate immune system recognizing and attacks foreign material. This is known as the foreign body reaction (FBR). Different materials are associated with different degrees of FBR. In the best-case scenario, the material is associated with only a minimal FBR and a mild, short-lived FBR occurs. In the worst-case scenario, a protracted severe FBR occurs. We are all familiar with the signs of a FBR, redness, warmth, swelling, pain, and loss of function. Indeed, medical students are given these words to memorize in latin: rubor, calor, tumor, dolor, functio laesa.

In their paper arguing for decreasing the amount of polypropylene implanted (deceasing the total amount of polypropylene used in a piece of mesh), Cobb et al state "The long-term consequences of implantable polypropylene prosthetics are not without concern. The body generates an intense inflammatory response to the prosthetic that results in scar plate formation, increased stiffness of the abdominal wall, and shrinkage of the biomaterial". This problem is well known in both the medical and scientific art. Multiple investigators have demonstrated the dramatic difference between a repair performed with native tissue and suture compared to one performed with polypropylene mesh. The authors demonstrated that, unlike the native tissue repair, the polypropylene (ppm) repair did not heal and continues to behave like both an acute and chronic wound.[153] Although decreasing

[153] U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL.

the inoculum (the amount of polypropylene) may decrease the severity of the FBR, the problem of the severe FBR with ongoing acute and chronic inflammation persists and may even worsen.[154] Acute and chronic inflammation are associated with both pain and loss of function.[155] Indeed the most common complication reported in the FDA's systematic review of transvaginal mesh are those associated with inflammation: extrusion and pain.

The Human Body Has and Adverse Effect on Polypropylene.

As described above as well as earlier in this report, polypropylene implantation creates a strong FBR. As part of the FBR the body's white blood cells release powerful oxidizing agents including ionized oxygen, hydrogen peroxide, and hypochlorite. These powerful oxidizing agents change the chemical composition and physical properties of the polypropylene mesh fibers. The oxidation of polypropylene mesh implants is many times greater than would be expected when exposed to room air.[156] This results in mesh

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103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.

[154] Arnaud Clavé & Hannah Yahi & Jean-Claude Hammou & Suzelei Montanari & Pierre Gounon & Henri Clavé. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261–270.
Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591. U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL. 103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.

[155] Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591

[156] Timothy C. Liebert,Richard P. Chartoff, Stanley L. Cosgrove, Robert S. Mccuskey. Subcutaneous Implants of Polypropylene Filaments. J. Biomed. Mater. Res. Vol. 10, Pp. 939-951 (1976)

degradation, worsening inflammation, loss of elasticity and contraction.[157] This contraction may be as great as 85% and continue for at least 9 years.[158] Even those studies frequently sited by purveyors of ppm have shown contraction in the range of 15 to 35% as well severe loss of elasticity.[159]

The Material Properties of the Gynemesh PS Polypropylene mesh are Not Appropriate for Vaginal Implantation.

Polypropylene mesh implantation in the treatment of abdominal hernias began decades prior to its use in vaginal surgery. Indeed, the original ppm implants used for vaginal surgery had obtained their 510K marketing approvals as abdominal hernia mesh implants or claimed such as predicates. Although ppm had been shown to decrease the recurrence rate of abdominal hernias, the loss of abdominal wall compliance and pain became a substantial problem. Prolonged patient discomfort and chronic pain were know to occur as often 20% and 50% of the time, respectively.[160] Looking at normal abdominal

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[157] C. R. Costello, S. L. Bachman, B. J. Ramshaw,2 S. A. Grant. Materials Characterization of Explanted Polypropylene Hernia Meshes. Journal of Biomedical Materials Research Part B: Applied Biomaterials. Published online 6 February 2007 in Wiley InterScience

[158] Letouzey V, Deffieux X, Levailolant J, et al . Overview of transvaginal placement of reconstructive materials (surgical mesh or biografts) for treatment of pelvic organ prolapse or stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:S205.

[159] Svabík, Kamil, Alois Martan, Jaromir Masata, Rachid El-Haddad, Petr Hubka, and Marketa Pavlikova. "Ultrasound Appearances after Mesh Implantation—evidence of Mesh Contraction or Folding?" International Urogynecology Journal Int Urogynecol J 22.5 (2010): 529-33. Dietz HP, Erdnaann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol. 2011;204:173.el-4.

[160] ÕDwyer PJ, Kingsnorth AN, Molloy RG, et al. Randomized clinical trial assessing impact of a lightweight or heavy- weight mesh o n chronic pain after inguinal hernia repair. Br J Surg 2005;92:166–170.Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591

wall compliance, Junge et all reported that hernia meshes should have at least 25% vertical stretching and 15% horizontal stretching.[161]

Although lighter weight ppm with increased compliance may decrease discomfort and pain, pain remains one of the most common complications following the implantation of ppm in the vagina. It is clear to even the non-physician non-scientist that the vaginal anatomy and function is quite different than that of the abdominal wall. The need for vaginal compliance is greater than that of the inguinal canal (the area of inguinal hernia repair). Substantial vaginal stretching is required for intercourse and childbirth. Hence, the 25% elasticity required for an abdominal hernia mesh may be insufficient for a vaginal mesh implant. Of even greater concern are the neurologic findings of Iakovlev. Iakovlev has demonstrated that transvaginal mesh explants have a nerve density on average 6 times higher than groin mesh explants and 11 times higher than mesh explants from the midline anterior abdominal wall. This alone can explain the high incidence of chronic pain associated with vaginal ppm implantation.[162]

Additionally, as described elsewhere herein, the foreign body reaction associated with ppm implantation leads to scaring and degradation with resultant contraction of the mesh. The variable rate and degree of contraction (15 to 85 percent over 3 months to 9 years) precludes a reliable method of predicting the final implant width and tension. This creates methodological problems including the inability of a surgeon explanting an infected PROSIMA from knowing if they have explanted the entirety of the PROSIMA®.

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[161] K. Junge á U. Klinge á A. Prescher á P. Giboni M. Niewiera á V. Schumpelick. Elasticity of the anterior abdominal wall and impact for reparation of incisional hernias using mesh implants. Hernia (2001) 5: 113±118

[162] In The United States District Court For The Southern District Of West Virginia Charleston Division In Re: Boston Scientific Corp. Pelvic Repair System Products Liability Litigation MDL No. 2326 Iakovlev General Expert Report

Decades in advance of the marketing of ppm mesh for transvaginal implantation; the abdominal hernia literature demonstrated a high incidence of severe inflammation, scarring, contraction and pain. Prior to the first sales of PROSIMA in the U.S. market, investigators had already shown that pore sizes of greater than 1000 microns were necessary to decrease contraction.[163] Yet, Ethicon chose not to measure its native poor size or effective poor size. As noted elsewhere in this monograph, Ethicon acknowledged that poore size had not been measured during product development, "Pore size in microns was not measured during the development of the Prolene Soft Mesh. The total percent area that is open was measured and is considered an accurate method. Since the product construction results in irregular pore geometries and size, it is not accurate to report a distinct pore size."[164] Additionally, prior to the marketing of PROSIMA, Ethicon's own studies had demonstrated that the Gynemesh PS of PROSIMA was associated with chronic inflammation and uniquely prone to deep erosion, seroma formation, and the loss of both collagen and elastin.[165] This later finding has been validated by recent investigation as well.[166] In addition, prior to the marketing of PROSIMA, Ethicon's paid consultants had demonstrated in Ethicon sponsored studies evidence of severe inflammation and contraction associated with GyneMesh PS.[167] This included a disclosure by Ethcion in its

[163] Muhl, et al. New Objective Measurement to Characterize the Porosity of Textile Implants. J. Biomed Mater Res Part B: Appl Biomater 84B:176-183, 2008

[164] ETH.MESH.01431617, 6-14/15-2006, email chain about Gynemesh PS/Prolene Soft mesh pore size, Robert Rousseau: (Ethicon principal engineer)

[165] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecol J 17.S1 (2006): 26-30.

[166] Liang, Rui, Wenjun Zong, Stacy Palcsey, Steven Abramowitch, and Pamela A. Moalli. "Impact of Prolapse Meshes on the Metabolism of Vaginal Extracellular Matrix in Rhesus Macaque." Obstetrical & Gynecological Survey 70.6 (2015): 385-87.

[167] Velemir, L., J. Amblard, B. Fatton, D. Savary, and B. Jacquetin. "Transvaginal Mesh Repair of Anterior and Posterior Vaginal Wall Prolapse: A Clinical and Ultrasonographic Study." Ultrasound in Obstetrics

2009 Prolift IFU of an observational study from 2004 on (gynemesh) cut like prolift (no trochars) that found **12.6%** moderate to severe contraction of vagina in French centers. (This was at 12 months).[168]

The severe inflammatory reaction and ongoing persistent chronic inflammation associated with the foreign body reaction was well known to cause a high incidence of vaginal Gynemesh PS erosion. Ethicon paid consultants had reported erosion rates ranging from 16% to 25%.[169] Jaquetin, one of the inventors of Ethicon's Prolift reported a 16% incidence of vaginal Gynemesh erosion. More than half of these patients were taken to surgical resection for this complication.[170] Of those not taken to surgical resection, only one resolved. The 29-month results of the uncontrolled observational PROSIMA study found a 10% incidence of mesh erosion and 73% of patients with this complication were taken to surgical intervention. As discussed elsewhere herein, a randomized controlled trial of a similar procedure found an initial erosion rate that was similar to that of the 1-Year

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and Gynecology Ultrasound Obstet Gynecol 35.4 (2010): 474-80., Svabík, Kamil, Alois Martan, Jaromir Masata, Rachid El-Haddad, Petr Hubka, and Marketa Pavlikova. "Ultrasound Appearances after Mesh Implantation—evidence of Mesh Contraction or Folding?" International Urogynecology Journal Int Urogynecol J 22.5 (2010): 529-33. , Dietz, Hans Peter, Max Erdmann, and Ka Lai Shek. "Mesh Contraction: Myth or Reality?" American Journal of Obstetrics and Gynecology 204.2 (2011): n. pag.

[168] ETH.MESH. 02341658

[169] Svabik K. Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014; 1-7. DOI: 10.1002/uog.13305., Lowman, JK. Does the Prolift system cause dyspareunia?, Am. J. Obstet. Gynecol. 199(6):707-712 (2008), Miller D., et al. Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse - 5-Year Results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143. Simone Dos Reis Brandão Da Silveira, Jorge Milhem Haddad, Zsuzsanna Ilona Katalin De Jármy-Di Bella, Fernanda Nastri, Miriam Goncalves Markos Kawabata, Silvia Da Silva Carramão, Claudinei Alves Rodrigues, Edmund Chada Baracat, and Antonio Pedro Flores Auge. "Multicenter, Randomized Trial Comparing Native Vaginal Tissue Repair and Synthetic Mesh Repair for Genital Prolapse Surgical Treatment." International Urogynecology Journal Int Urogynecol J 26.3 (2014): 335-42., Withagen, Mariëlla I., Mark E. Vierhout, Jan C. Hendriks, Kirsten B. Kluivers, and Alfredo L. Milani. "Risk Factors for Exposure, Pain, and Dyspareunia After Tension-Free Vaginal Mesh Procedure." Obstetrics & Gynecology 118.3 (2011): 629-36.

[170] Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." International Urogynecology Journal Int Urogynecol J 24.10 (2013): 1679-686.

PROSIMA study only to find a doubling of the erosion rate at three-year follow-up. Other authors have demonstrated that overall mesh extrusion rate increases with time.[171]

The severe foreign body related inflammatory reaction with persistent chronic inflammation and associated fibrosis and contraction results in a high incidence of dyspareunia that is uniquely difficult to treat, often resulting in loss of consortium in perpetuity.[172] Ethicon paid consultants have reported de novo dyspareunia rates ranging from 16% to 26%.[173] Jacquetin, another paid Ethicon consultant, prospectively evaluated 323 women implanted with Gynemesh PS and found a 17% incidence of de novo dyspareunia in the mesh group and a 2% incidence in the native tissue group.

Based on my knowledge, training, experience, review of the medical, and scientific literature, and review of internal documents I state with a reasonable degree of medical that for numerous causes including but not limited to the severe and chronic foreign body reaction associated with transvaginal polypropylene mesh, the poor post-implantation compliance of polypropylene mesh with resultant material tissue mismatch, the known high and difficult to treat incidence of de novo dyspareunia associated with the transvaginal implantation of polpyproylene mesh and, more exactly, Gynemesh PS, the high incidence of mesh erosion and contraction associated with Gynemesh PS, and the insufficient poor

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[171] De Tayrac R, Eglin G, Villard P, et al. Anatomical and functional assessment of prolapse repair by vaginal route using a collagen coating polypropylene mesh. A french prospective multicentre study. 3-year results. Iut Urogynecol J (2008) 19 (Supp11):S96

[172] Crosby, Erin C., Melinda Abernethy, Mitchell B. Berger, John O. Delancey, Dee E. Fenner, and Daniel M. Morgan. "Symptom Resolution After Operative Management of Complications From Transvaginal Mesh." Obstetrics & Gynecology 123.1 (2014): 134-39. Web.

[173] Withagen, Mariëlla I., Mark E. Vierhout, Jan C. Hendriks, Kirsten B. Kluivers, and Alfredo L. Milani. "Risk Factors for Exposure, Pain, and Dyspareunia After Tension-Free Vaginal Mesh Procedure." Obstetrics & Gynecology 118.3 (2011): 629-36. Lowman, Joye K., Leticia A. Jones, Patrick J. Woodman, and Douglass S. Hale. "Does the Prolift System Cause Dyspareunia?" American Journal of Obstetrics and Gynecology 199.6 (2008): 707e1-8

size of Gynemesh PS I say with a reasonable degree of medical certainty that the PROSIMA Gynemesh PS material was defective.

Dated: Feb. 1, 2016

Ralph Zipper, M.D. , FACOG FPMRS

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Realized results represent complications that have occurred and have either been documented in the FDA MAUDE database, reported in the medical literature, or complications I have evaluated and often treated in my pelvic medicine center. Many of these realized results represent failure related harm that was not evaluated by Ethicon in its FEMA.
ETH-07252, ETH-07282
ETH.07294
See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey, Exhibit 621
See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey
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The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notification. July 28, 2014 CDRH. FDA defines “Intended Use” as: The term “intended uses” refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the circumstances surrounding the distribution of the device. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such representatives. It may be shown by the offering or the using of the device, with the knowledge of such persons or their representatives, for a purpose for which it is neither labeled nor advertised. The general statement of the “Indications for Use” identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device. The Indications for Use statement, as defined by the FDA, has a very defined structure. The Intended Use on the other hand is a regulatory term that describes an overall picture. https://alwaysincompliance.wordpress.com/2011/09/02/intended-use-vs-indications-for-use/

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ETH.MESH.00401366,57,59,63,65,66	
ETH.MESH.00401354 The choice of 20% as the maximum rate of recurrence was developed following a literature review and discussions with experts in the field of pelvic floor repair (urologists and urogynecologists).	
ETH.MESH.00012061	
This number is corrected for un-related re-operations such as cholecystecomy, femur fracture, and examination under anesthesia). ETH.MESH.00012064-68	
3 new cases of dyspareunia reported amongst 40 sexually active patients.	http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/
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ETH.MESH.00401470-71. Ethicon's CONFIDENTIAL STATISTICAL ANALYSIS PLAN stipulated that all missing data would be considered a recurrence at that such data would be utilized for confirmatory analysis. Additionally, several patients seem to have been counted as failures at 6 months but not at one year. The inclusion of these patients as failures would further increase the failure rate ETH-75916-75917; ETH-75591-75592. Dr. David Robinson, one of the 3 investigators of the U.S. TVM study serves employed by Ethicon as its World Wide Medical Director from November of 2005 to December of 2010. (https://www.linkedin.com/in/davidrobinson21). Dr. Lucente was a paid consultant of Ethicon since January 21st of 2005 and would get paid to lecture and train surgeons on PROLIFT. ETH.MESH.00366804.
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These investigators did not disclose the POP-Q scores of the women who met the failure definition. However, they did report that the mean POP-Q of the entire native tissue group at 12 months. Point Aa was -1.5 +/-1.4. Point Ba was -1.6 +/- 1.5. The simple math tells us that, within 2 standard deviations of the mean, not a single patient had prolapse beyond the hymenal ring. Five percent of 97 women would fall outside this range, 2.5% above and 25% below. Hence, less than 3 women in the no-mesh group were beyond the hymenal ring. Those 1 or 2 women beyond the hymenal ring may very well have still been POP-Q stage 2. “Despite better anatomic results, the mesh tech- nique in our hands did not resolve patents’ symptoms more frequently than the traditional technique. This reflects the fact that the majority of stage II recur- rences are asymptomatic.”.	
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See table 2 of study.
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61 women were sexually active prior to TVM. 40 were sexually active at 1 year after implant. 39 are sexually active at 3 years.
13 women suffered mesh extrusion. A total of six had undergone excision (5 at one year and one now). If we allow that excisions resulted in cure, 5 of the 7 patients not excised of their extrusion (71%) are with persistent mesh extrusion. Of course it is possible that excisions failed and the 46% overall persistent extrusion rate represents a combination of excisional failures and medical failures. 85 women available at 3 year follow-up
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The authors state in their discussion that the anatomic success rate was 81.2% but this is not supported by their data, calculation, or reports throughout this manuscript of 20.2 percent failure.
James D. Dziuraa, Lori A. Posta, Qing Zhaob, Zhixuan Fub, ,and Peter Peduzzib. Strategies for dealing with Missing data in clinical trials: From design to Analysis. Yale Journal Of Biology And Medicine 86 (2013), Pp.356. James Carpenter. Statistical modelling with missing data using multiple imputation.Lecture 2: Ad-hoc methods and introduction to multiple imputation. Pg.5-6
ETH.MESH.00401472
By stating that only 4.7% of mesh extrusions remained present, the authors mislead the reader to believe that 95.3% of mesh extrusions resolved. The 4.7% however represents the number of remaining and asymptomatic mesh extrusion as a fraction of the total study population and not as a fraction of those that had a mesh extrusion.
Jacquetin, Bernard, Brigitte Fatton, Claude Rosenthal, Henri Clavé, Philippe Debodinance, Piet Hinoul, Judi Gauld, Olivier Garbin, Juan Berrocal, Richard Villet, Delphine Salet Lizée, and Michel Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 3-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecol J</i> 21.12 (2010): 1461
Conflicts of interest: Bernard Jacquetin holds the patent for Prolift, for which he receives royalties from Ethicon. B. Jacquetin, B. Fatton, C. Rosenthal, H. Clave, P. Debodinance, O. Garbin, J. Berrocal, R. Villet, D. Salet Lizee and M. Cosson all have had consultancy positions for Ethicon. P. Hinoul and J. Gauld are employed by Ethicon. This disclosure appears at the end of the article cited #217
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See Deopsition of Paul Parisi. Patricia Hammons v. Ethicon Womens Health and Urology.1/12/24. 766:15-767:23 and 769:14-24. See ETH.18412
The authors report that 70% of the 20 women with extrusions were resected. Of these 14 women, 8 were resected in the O.R.. Hence another 6 were resected outside the O.R.
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ETH.MESH.03960116 “If required, small reductions in the dimensions ofthe Total Implant to ensure proper fit should be performed at this point” .ETH.MESH.00658367-68. “While inexperienced surgeons initially may look for smaller pieces of mesh, the larger piece of mesh ¡s necessary to prevent bearing down on the vaginal capacity during healing”. “This loose placement of mesh is often counterintuitive to the first time surgeon but is valuable in maintaining vaginal length”.
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The authors herein defined composite success as: “leading edge above the hymen (<0) and no bulge symptoms” The Ethicon study protocol defined reintervention as repeat surgery for prolapse and did not include pessary use for recurrent POP symptoms.
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Please see my discussion of the 3-year data abstract and full manuscript that demonstrates six women with de-novo dyspareunia. Those 6 women plus the three described with de novo dyspareunia at 5 years results in up to 9 (of 33 sexually active women) with de novo dyspareunia).
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Id

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Id
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“These problems (mesh extrusion) arise due to exposure of the mesh material caused by inadequate healing”. Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20.
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ETH.01786
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ETH.00264
The statement of “very small incisions in the vagina” also appears in the patient advertisement piece, ETH.00264

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See depositon of David Robinson. 376:14-24		
See deposition of Scott Jones pg 718, 729,731-734		
ETH.59475-59508		
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ETH.MESH.04098598	Prosima Study Conference Call Meeting Minutes	8/9/2007
ETH.MESH.03294572-581	Project Plan	8/12/2007

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ETH.MESH.05009194-96	Email re: ProLift + M Registration	4/28/2008
ETH.MESH.03164735	Email re Prosima v Colporraphy	8/27/2009
ETH.MESH.04569706	Email re: Prosima Communication and Action Plan	4/11/2008
HMESH_ETH_02684590	Powerpoint: Gynecare Prosima Launch Readiness	5/12/2009
ETH.MESH.00057757	2009 Incontinence & Pelvic Floor Summit	02/06-08/2009
ETH.MESH.02156725	Email re: PROSIMA Feedback	2/8/2009

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ETH.MESH.02156777	Email re: Prosima	2/9/2009
ETH.MESH.01186129-131	Email re: PROSIMA Feedback	2/9/2009
ETH.MESH.02156759-760	Email re: PROSIMA Feedback	2/9/2009
ETH.MESH.00548923	Email re: PROSIMA Feedback	2/10/2009
ETH.MESH.11832807-08	Email re: Summit Recap	2/11/2009
ETH.MESH.05095524	Email re: As Requested: PROSIMA Feedback	2/12/2009

ETH.MESH.00794750	Email re: 1 Million Dollars!!!	4/19/2010
ETH.MESH.07378350-52	E-APEX Marketing Excellence Award Submission Form	9/30/2010
ETH.MESH.02252055-57	Email FW: Pelvic Floor Mesh	10/25/2010
ETH.MESH.03643257	Powerpoint: Ethicon US 2011 Brand Business Plan	1/7/2011
ETH.MESH.03686819	Email Fw: ACTION: Ethicon Global Alignment Meeting Inviation and Registration	2/4/2011

ETH.MESH.08966061-64	Email re: Marketing Mastery Submission TA Prosima Proof & Attached Award Submission Form	10/31/2011
ETH.MESH.05563395-98	Email re: AW Prosima+M Deliverables for 510k submission	1/31/2011
ETH.MESH.05572810	Email re: couple of things	4/4/2011
ETH.MESH.03360404	Email and attached slides re LV Prosima+M_ Regulatory slide SBT for 7th of June	6/3/2011
ETH.MESH.07903682	Email re: PS vs +M	6/30/2011

ETH.MESH.09268043	Email re: Corp Info on Compensation to HCP	11/15/2004
ETH.MESH.10376374	Email re Lab, etc.	2/28/2007
ETH.MESH.00070065	Calendar Meeting: IFU last minute changes	2/20/2008
ETH.MESH.05134613	Email re: Prosima	6/22/2009
ETH.MESH.10416655	Email re Reporting Prosima Successs	11/11/2009
ETH.MESH.08961175	Email re: Prosima Apical Support Learning Guide	6/17/2010
ETH.MESH.03898831-34	Email re: 2011 VOTE Team Conf Call-VOTE Team Questions	3/7/2011
ETH.MESH.05805807	Letter "Dear Colleagues"	4/11/2011

ETH.MESH.05566117	Powerpoint: Reshaping Regulatory to Better Meet Ethicon's Strategic Goals	4/12/2011
ETH.MESH.03466382	Email re: Dr. Bedestani	5/12/2011
ETH.MESH.05592152	Email re: QBR 4/20	5/20/2011
ETH.MESH.04476164	Powerpoint: EWHU Board Meeting	6/13/2011
ETH.MESH.03643727	Email re: Mid-Year Note 2011: Urogynecology and Reconstuctive Pelvic Surgery Group	6/27/2011
ETH.MESH.03721558	Focus on Mesh Exposure - Road to Improvement	12/21/2011